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L2 ANSWER 1 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2000:358043 BIOSIS
DN PREV200000358043
TI The fusion protein MEN 11303 (granulocyte-macrophage colony-stimulating factor/erythropoietin) acts as a potent inducer of erythropoiesis.
AU Battaglia, Alessandra (1); Fattorossi, Andrea; Pierelli, Luca; Bonanno, Giuseppina; Marone, Maria; Ranelletti, Franco O.; Coscarella, Annamaria; ***De Santis, Rita*** ; Bach, Simona; Mancuso, Salvatore; Scambia, Giovanni
CS (1) Ist. Ostetricia e Ginecologia, Universita Cattolica del Sacro Cuore, L.go A. Gemelli 8, 000168, Roma Italy
SO Experimental Hematology (Charlottesville), (May, 2000) Vol. 28, No. 5, pp. 490-498. print.
ISSN: 0301-472X.
DT Article
LA English
SL English
AB Objective: A fusion protein made of human granulocyte-macrophage colony-stimulating factor (GM-CSF) and erythropoietin (EPO), referred to as MEN 11303, has been tested for biologic activity using mobilized CD34+ cells. Methods and Results: MEN 11303 and a combination of GM-CSF/EPO produced the same amount of colony-forming unit granulocyte-macrophage (CFU-GM), of burst-forming unit erythroid (BFU-E), and of multipotent CFU-mixed. After 15 days, liquid cultures of CD34+ cells exposed to MEN 11303 yielded a total cell number larger than that obtained with an equimolar mixture of GM-CSF and EPO, with a clear prevalence of cells exhibiting an erythroid phenotype. A colony-forming cell assay established from CD34+ cells precultured with MEN 11303 for 7 days yielded a greater amount of BFU-E than GM-CSF/EPO combination. Exposing CD34+ cells to MEN 11303 for 7 days in liquid culture resulted in higher recoveries of cells expressing a comparatively less differentiated hematopoietic phenotype and of long-term culture initiating cells. A cell-based binding-competition assay using the human EPO-receptor (EPO-R) transfected murine Ba/F3EPOR cell line showed that MEN 11303 bound to EPO-R with a sixfold lower affinity but induced a more sustained receptor phosphorylation. MEN 11303 supported the growth of Ba/F3EPOR cells more efficiently than EPO and remained detectable in the spent culture medium for a longer time. Conclusion: MEN 11303 and the combination of GM-CSF/EPO are equally potent in recruiting hematopoietic progenitors into cycle, but the fusion protein is superior in promoting the expansion of committed erythroid percursors. Primitive hematopoiesis is less affected by MEN110303 than GM-CSF/EPO combination. Part of these effects may reflect the peculiar interaction of the EPO moiety of MEN 11303 with the EPO-R.

L2 ANSWER 2 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2000:32154 BIOSIS
DN PREV200000032154
TI Expansion of granulocyte colony-stimulating factor/chemotherapy-mobilized CD34+ hematopoietic progenitors: Role of granulocyte-macrophage colony-stimulating factor/erythropoietin hybrid protein (MEN11303) and interleukin-15.
AU Pierelli, Luca (1); Scambia, Giovanni; Bonanno, Giuseppina; Coscarella, Annamaria; ***De Santis, Rita*** ; Mele, Antonio; Battaglia, Alessandra; Fattorossi, Andrea; Romeo, Virgilio; Menichella, Giacomo; Mancuso, Salvatore; Leone, Giuseppe
CS (1) Servizio di Ematologia ed Emotrasfusione, Universita Cattolica del Sacro Cuore, Largo A. Gemelli 8, 00168, Roma Italy
SO Experimental Hematology (Charlottesville), (March, 1999) Vol. 27, No. 3, pp. 416-424.
ISSN: 0301-472X.
DT Article
LA English
SL English
AB Ex vivo stroma-free static liquid cultures of granulocyte colony-stimulating factor (G-CSF)/chemotherapy-mobilized CD34+ cells were established from patients with epithelial solid tumors. Different culture conditions were generated by adding G-CSF, granulocyte-macrophage colony-stimulating factor (GM-CSF), Flt3 ligand (Flt3), megakaryocyte growth and development factor (Peg-rHuMGDF), GM-CSF/erythropoietin (EPO) hybrid protein (MEN11303), and interleukin-15 (IL-15) to the basic stem cell factor (SCF) + interleukin-3 (IL-3) + EPO combination. This study showed that, among the nine different combinations tested in our 5% autologous plasma-containing cultures, only those containing IL-3/SCF/Flt3/MEN11303 and IL-3/SCF/Flt3/MEN11303/IL-15 significantly expanded colony-forming unit granulocyte-macrophage (CFU-GM), burst-forming unit erythroid (BFU-E), long-term culture-initiating cells (LTC-IC), CD34+, and CD34+/CD38- cells after 14 days of culture. Particularly, the addition of IL-15 toIL-3/SCF/Flt3/MEN11303 combination produced a significant increase of LTC-IC, with an average 26-fold amplification as compared to input cells, without any detrimental effect on CFU-GM and BFU-E expansion. This combination also produced a statistically significant 3.6-fold expansion of primitive CD34+/CD38- cells. Moreover, this study confirms the previously described

erythropoietic effect of MEN11303, which, in our experience, was the only factor capable of expanding BFU-E. Compared to equimolar concentrations of GM-CSF and EPO, MEN11303 hybrid protein showed a significantly higher capacity of expanding CFU-GM, BFU-E, LTC-IC, CD34+, and CD34+/CD38- cells
when these cytokines were tested in combination with IL-3/SCF/Flt3. These cultures indicated that Peg-rHuMGDF addition to IL-3/SCF/EPO/Flt3 does not affect CFU-GM and BFU-E expansion but, unlike G-CSF or GM-CSF, it does not decrease the ability of Flt3 to expand primitive LTC-IC. These studies indicate that, starting from G-CSF/chemotherapy-mobilized CD34+ cells, concomitant expansion of primitive LTC-IC, CFU-GM, BFU-E, CD34+, and CD34+/CD38- cells is feasible in simple stroma-free static liquid cultures, provided IL-3/SCF/Flt3/MEN11303/IL-15 combination is used as expanding cocktail in the presence of 5% autologous plasma.

L2 ANSWER 3 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:423786 BIOSIS
DN PREV199900423786
TI Purification and characterization of two recombinant human granulocyte colony-stimulating factor glycoforms: Pharmacokinetic and activity studies of single-dose administration in mice.
AU Rotondaro, Luigi (1); De Paolis, Enrico; Ferrero, Dario; D'Alatri, Laura; Raucci, Giuseppe; Fabbri, Armando; Gerwig, Gerrit J.; Kamerling, Johannis P.; Mariani, Maurizio F.; Mele, Antonio; ***De Santis, Rita***
CS (1) Department of Biotechnology, Menarini Ricerche S.p.A., Via T. Speri 10, 00040, Pomezia, Roma Italy
SO Molecular Biotechnology, (April, 1999) Vol. 11, No. 2, pp. 117-128. ISSN: 1073-6085.
DT Article
LA English
SL English
AB Two recombinant human granulocyte colony-stimulating factor (rhG-CSF) isoforms were isolated from the medium conditioned by an engineered Chinese hamster ovary (CHO) cell line. The two rhg-CSFs were characterized and were found to differ in the carbohydrate structure attached to Thr-133. The glycoform, referred to as Peak 1, contains the O-linked glycan Neu5Ac(alpha2-3)Gal(beta1-3)GalNAc; the Peak 2 glycoform contains the O-linked glycan Neu5Ac(alpha2-3)Gal(beta1-3)(Neu5Ac(alpha2-6))GalNAc. The two glycoforms displayed a similar biological activity in cultures of a mouse 32D C13 cell line and human bone-marrow myelo-monocytic progenitor
cells (CFU-GM). In the latter test both glycoforms displayed a higher activity than nonglycosylated rMet-hG-CSF from Escherichia coli. The pharmacokinetic profile and activity of the two rhg-CSF glycoforms and of a mixture of them (Pool) were investigated in mice treated with a single injection of rhg-CSF at the doses of 125 mug and 250 mug/kg, given via the intravenous (iv) and the subcutaneous (sc) route, respectively. The plasma concentration profiles obtained were similar for all three substances and did not show any relevant differences in absorption or elimination. The pharmacokinetic parameters indicate that the three substances have similar area under the curve (AUCs), volumes of distribution, and terminal half-life. Furthermore, our data indicate a high bioavailability of the two different glycoforms of rhg-CSF when given to mice via the sc route either singularly or as a mixture. Detectable levels of rhg-CSF persisted for more than 8 h in the iv and more than 24 h in the sc route of administration. All three substances induced early neutrophilia in mice. All rhg-CSF-treated mice developed a two-four-fold rise in neutrophil counts as early as 4 h after the intravenous and 2 h after the subcutaneous injection. Relatively high levels of neutrophils were maintained for at least 8 and 24 h after iv and sc administration, respectively.

L2 ANSWER 4 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:416361 BIOSIS
DN PREV199900416361
TI Recombinant production of fusion proteins comprising erythropoietin and GM-CSF components.
AU Mele, Antonio (1); ***De Santis, Rita*** ; Carloni, Cristina; Coscarella, Annamaria
CS (1) Montecatini Terme Italy
ASSIGNEE: Menarini Ricerche S.p.A.
PI US 5916773 Jun. 29, 1999
SO Official Gazette of the United States Patent and Trademark Office Patents, (Jun. 29, 1999) Vol. 1223, No. 5, pp. NO PAGINATION. ISSN: 0098-1133.
DT Patent
LA English

L2 ANSWER 5 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:172768 BIOSIS
DN PREV199900172768
TI The rhGM-CSF-EPO hybrid protein men 11300 induces anti-EPO antibodies and
severe anaemia in rhesus monkeys.
AU Coscarella, Annamaria (1); Liddi, Roberto; Di Loreto, Mario; Bach, Simona; Faiella, Angela; van der Meide, Peter H.; Mele, Antonio; ***De Santis,*** *** Rita***
CS (1) Department of Biotechnology Research, Menarini Ricerche S.p.A., Via Tito Speri 10-00040 Pomezia, Rome Italy
SO Cytokine, (Dec., 1998) Vol. 10, No. 12, pp. 964-969. ISSN: 1043-4666.
DT Article
LA English
AB A recombinant human GM-CSF-EPO hybrid protein named MEN 11300 was administered biweekly for a total of 6 weeks to rhesus monkeys in order to evaluate its pharmacokinetic behaviour, tolerability and immunogenicity. In this primate species a strong antibody response was induced which neutralized the in vitro biological activity of human EPO while no antibody response could be detected against human GM-CSF. A severe drop in reticulocyte counts at approximately 2 weeks after initiation of treatment was followed by a dramatic decrease in the number of erythrocytes. No effects were observed on GM-CSF-dependent hematopoietic lineages and the clinical chemistry analyses did not reveal signs of general toxicity. Reticulocyte and erythrocyte counts started to recover 3-4 weeks after discontinuation of treatment in concert with a decline in anti-EPO antibody titres. Nevertheless, cell numbers remained below basal levels up to 50 days after the last MEN 11300 administration. Haematological impairment indicates that the administration to non-human primate of human EPO fused to human GM-CSF, induces neutralizing autoantibodies to the self EPO. Present data do not allow prediction of the immunogenic potential of the fusion protein in humans and a dose-escalating phase I study should be addressed to investigate the safety of the product.

L2 ANSWER 6 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:46828 BIOSIS
DN PREV199900046828
TI Production and characterisation of a recombinant single-chain anti ErbB2-clavin immunotoxin.
AU D'Alatri, Laura; Di Massimo, Anna Maria; Anastasi, Anna Maria; Pacilli, Aurelio; Novelli, Sabrina; Saccinto, Maria Pia; ***De Santis, Rita*** ; Mele, Antonio; Parente, Dino (1)
CS (1) Dep. Biotechnol., Menarini Ricerche S.p.A., via Tito Speri 10, 00040 Pomezia, Rome Italy
SO Anticancer Research, (Sept.-Oct., 1998) Vol. 18, No. 5A, pp. 3369-3373. ISSN: 0250-7005.
DT Article
LA English
AB We generated a recombinant immunotoxin, named scFv(MGR6)-Cla, composed of
the Fv region of an anti ErbB2 monoclonal antibody (MGR6) fused to clavin, a type I ribosome-inactivating protein (RIP) from Aspergillus clavatus. ErbB2 is a tyrosine kinase receptor which is overexpressed in most adenocarcinomas; clavin is a 17 kDa ribonuclease which inhibits protein synthesis by inactivating ribosomes. A recombinant DNA construct containing the cDNA of the single chain Fv fragment (scFv) of the MGR6 antibody fused to the clavin cDNA, was expressed at high levels in Escherichia coli as an insoluble fusion protein containing an N-terminal affinity tag of six consecutive histidine residues. Inclusion bodies were denatured and the recombinant fusion protein was purified under denaturing conditions by single-step purification using immobilized metal ion affinity chromatography (IMAC). The purified immunotoxin was renaturated at high yield and histidine tag removed by digestion with enterokinase. The purity of the immunotoxin obtained after refolding was confirmed by SDS-PAGE, RP-HPLC, GPC-HPLC and N-terminal sequence analysis. Cell-free protein synthesis inhibition and binding assays showed that both clavin and scFv(MGR6) maintained their properties after refolding.

L2 ANSWER 7 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1999:13788 BIOSIS
DN PREV199900013788
TI Pharmacokinetic and immunogenic behavior of three recombinant human GM-CSF-EPO hybrid proteins in cynomolgus monkeys.
AU Coscarella, Annamaria (1); Liddi, Roberto; Bach, Simona; Zappitelli, Sabrina; Urso, Renato; Mele, Antonio; ***De Santis, Rita***
CS (1) Biotechnol. Res. Dep., Menarini Ricerche S.p.A., Via Tito Speri 10, 00040 Pomezia, Rome Italy
SO Molecular Biotechnology, (Oct., 1998) Vol. 10, No. 2, pp. 115-122. ISSN: 1073-6085.
DT Article
LA English
AB MEN 11300, MEN 11301, and MEN 11303 are three recombinant human hybrid
proteins that, as has recently been described, induce in vitro erythroid differentiation. This article provides data on their pharmacokinetic and immunogenic behavior after repeated iv administration to cynomolgus monkeys at 0.8 or 1.6 mug/kg doses. Pharmacokinetic data, obtained after the first administration, showed that the half-life (t1/2) and clearance (CL) values are dose dependent, with no significant differences among the three hybrid proteins. After the tenth administration, MEN 11300 and MEN 11301, both at high and low dose, and MEN 11303 at high dose were undetectable in plasma, whereas MEN 11303 at the lower dose showed no alteration in its pharmacokinetic profile. Immunologic analyses of plasma provided an explanation for this different pharmacokinetic behavior. In fact, plasma samples from animals treated repeatedly with MEN 11300 and MEN 11301 showed specific antibody formation in response to both the high- and the low-dose regimens. These antibodies exerted in vitro a strong neutralizing activity of the hybrid proteins, with a predominant specificity for the erythropoietin (EPO) portion. By contrast, MEN 11303 at the lower dose did not induce a detectable antibody response whereas the antibodies observed on the high-dose regimen did not exert neutralizing activity against the hybrid proteins nor against

granulocyte-macrophage colony-stimulating factor (GM-CSF) or EPO. Hematologic parameters were not affected by the treatments, thus indicating that the anti-EPO neutralizing antibody response does not cross react with the endogenous monkey cytokine. The overall immunogenicity data suggest that among the three fusion proteins, MEN 11303 could have a lower immunogenic potential.

L2 ANSWER 8 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:400713 BIOSIS
DN PREV199800400713
TI Structural characterization and independent folding of a chimeric glycoprotein comprising granulocyte-macrophage colony stimulating factor and erythropoietin sequences.
AU Amoresano, Angela (1); Andolfo, Annapaola (1); Siciliano, Rosa Anna; Mele, Antonio; Coscarella, Annamarie; ***De Santis, Rita*** ; Mauro, Sandro; Pucci, Piero; Marino, Gennaro
CS (1) Cent. Int. Serv. Spettrometria Massa, Via Pansini 5, 80131 Napoli Italy
SO Glycobiology, (Aug., 1998) Vol. 8, No. 8, pp. 779-790. ISSN: 0959-6658.
DT Article
LA English
AB MEN 11300 is a hybrid glycoprotein of 297 amino acids obtained by fusion of the cDNA encoding GM-CSF with the cDNA encoding EPO followed by transfection of the hybrid gene into CHO cells. The oligonucleotide construct incorporated a spacing sequence between the two individual cDNAs which encodes eight amino acids constituting a linker peptide intended to separate the GM-CSF and EPO moieties. The recombinant MEN 11300 protein was submitted to a detailed structural characterization including the verification of the entire amino acid sequence, the assignment of the disulfide bridges pattern, the identification of the glycosylation sites and the definition of the glycosidic moiety, including site-specificity. Partial processing of the C-terminal Arg residue and the occurrence of N-glycosylation sites at Asn27, Asn155, Asn169, Asn214 were established. Moreover, O-glycosylation at Ser257 and at the N-terminal region was also detected. A large heterogeneity was observed in the N-glycans due to the presence of differently sialylated and fucosylated branched complex type oligosaccharides whereas O-linked glycans were constituted by GalGalNAc chains with a different number of sialic acids. The disulfide bridges pattern was established by direct FABMS analysis of the proteolytic digests or by ESMS analysis of HPLC purified fractions. Pairing of the eight cysteine residues resulted in Cys54-Cys96, Cys88-Cys121, Cys138-Cys292, and Cys160-Cys164. This S-S bridges pattern is identical to that occurring in the individual natural GM-CSF and EPO, thus showing that the two protein moieties in MEN 11300 can independently acquire their native three-dimensional structure.

L2 ANSWER 9 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:345803 BIOSIS
DN PREV199800345803
TI Overproduction of soluble, extracellular cytotoxin alpha-sarcin in Escherichia coli.
AU Parente, Dino (1); Raucci, Giuseppe; D'Alatri, Laura; D'Estais, Guy; Novelli, Sabrina; Pacilli, Aurelio; Saccinto, Maria Pia; Mele, Antonio; ***De Santis, Rita***
CS (1) Menarini Ricerche, S.p.A., Dep. Biotechnol., Via T. Speri, 10, 00040 Pomezia Italy
SO Molecular Biotechnology, (April, 1998) Vol. 9, No. 2, pp. 99-106. ISSN: 1073-6085.
DT Article
LA English
AB The goal of the present study was to establish the condition to obtain preparative amounts of the recombinant cytotoxin alpha-sarcin to be used for immunoconjugate production. alpha-Sarcin cDNA was isolated from Aspergillus gigantea strain MDH 18894 and its expression in Escherichia coli was attempted by the use of both two-cistron and fusion protein-expression systems. Whereas the former resulted in low intracellular expression level of recombinant alpha-sarcin (r-Sar), the latter allowed high-level expression of the fusion protein in the culture supernatant. A variant form of alpha-sarcin with an additional threonine residue in position 1 (Thr-Sar) was obtained by proteolytic processing of the fusion protein with a final yield after purification of 40 mg/L of culture. Both recombinant proteins r-Sar and Thr-Sar were identical to native a-sarcin with respect to the biochemical properties and to the in vitro biological activity.

L2 ANSWER 10 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1998:274279 BIOSIS
DN PREV199800274279
TI Role of cross-linking agents in determining the biochemical and pharmacokinetic properties of Mgr6-clavin immunotoxins.
AU Dosio, Franco; Arpicco, Silvia; Adobati, Elena; Canevari, Silvana; Brusa, Paola; ***De Santis, Rita*** ; Parente, Dino; Pignanelli, Paola; Negri, Donatella R. M.; Colnaghi, Maria I.; Cattel, Luigi (1)
CS (1) Dipartimento Sci. Technologia Farmaco, Univ. Torino, Torino Italy
SO Bioconjugate Chemistry, (May-June, 1998) Vol. 9, No. 3, pp. 372-381. ISSN: 1043-1802.
DT Article
LA English
AB Several immunotoxins (ITs) were synthesized by the attachment of clavin, a recombinant toxic protein derived from Aspergillus clavatus, to the monoclonal antibody Mgr6 that recognizes an epitope of the gp 185HER-2 extracellular domain expressed on breast and ovarian carcinoma cells. Conjugation and purification parameters were analyzed in an effort to optimize the antitumor activity and stability of the ITs in vivo. To modulate the in vitro and in vivo properties of the immunotoxins, different coupling procedures were used and both disulfide and thioether linkages were obtained. Unhindered and hindered disulfide with a methyl group linkage ethyl S-acetyl 3-mercaptopropionthioimidate ester hydrochloride (AMPT) or ethyl S-acetyl-3-mercaptobutyrothioimidate ester hydrochloride (M-AMPT) were obtained by reaction with recombinant clavin, while the monoclonal antibody Mgr6 was derivatized with ethyl-3((4-carboxamidophenyl)dithio)propionthioimidate ester hydrochloride (CDPT). To achieve higher hindrance (a disulfide bond with a germinal dimethyl group), Mgr6 was derivatized with the N-hydroxysuccinimidyl 3-methyl-3-(acetylthio)butanoate (SAMBA) and clavin with CDPT. To evaluate the relevance of the disulfide bond in the potency and pharmacokinetic behavior of the ITs, a conjugate consisting of a stable thioether bond was also prepared by derivatizing Mgr6 with the N-hydroxysuccinimidyl ester of iodoacetic acid (SIA) and clavin with AMPT. The immunotoxins were purified and characterizing used a single-step chromatographic procedure. Specificity and cytotoxicity were assayed on target and unrelated cell lines. The data indicate that the introduction of a hindered disulfide linkage into ITs has little or no effect on antitumor activity and suggest that disulfide cleavage is essential for activity; indeed, the intracellularly unbreakable thioether linkage produced an inactive IT. Analysis of IT stability in vitro showed that the release of mAb by incubation with glutathione is proportional to the presence of methyl groups and increases exponentially with the increase in steric hindrance. Analysis of the pharmacokinetic behavior of ITs in Balb/c mice given intravenous bolus injections indicated that ITs with higher in vitro stability were eliminated more slowly, i.e., the disulfide bearing a methyl group doubled the beta-phase half-life (from 3.5 to 7.1 h) compared with that of the unhindered, while a germinal dimethyl protection increased the elimination phase to 24 h. The thioether linkage showed its intrinsic stability with a beta-phase half-life of 46 h. The thioether linkage also increased the distribution phase from 17 to 32 min. The in vitro characteristics and in vivo stability of Mgr6-clavin conjugates composed of a methyl and dimethyl steric hindered disulfide suggest clinical usefulness.

L2 ANSWER 11 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1997:120184 BIOSIS
DN PREV199799426687
TI Expression and characterization of a mouse/human chimeric antibody specific for EGF receptor.
AU Ferrer, Cristina (1); Anastasi, Anna M.; Di Massimo, Anna M.; Bullo, Angela; Di Loreto, Mario; Raucci, Giuseppe; Pacilli, Aurelio; Rotondaro, Luigi; Mauro, Sandro; Mele, Antonio; ***De Santis, Rita***
CS (1) Menarini Ricerche SpA, Dep. Biotechnol., Via Tito Speri 10, 00040 Pomezia, Rome Italy
SO Journal of Biotechnology, (1996) Vol. 52, No. 1, pp. 51-60. ISSN: 0168-1656.
DT Article
LA English
AB Murine antibodies which recognize the epidermal growth factor receptor (EGF-r) are good candidates for therapy and diagnosis of tumours overexpressing this receptor. Here we report the isolation of the variable regions from a murine monoclonal antibody anti-EGF-r (Mint5), the procedure to obtain the mouse/human chimeric antibody (chMint5) and its expression in COS, NSO and CHO cells. The approach followed to construct chMint5 is based on the use of consensus primers specific for the ends of the variable regions. The sequence imposed by the primers did not affect the targeting potential of the antibody. In fact, the affinity of the chimeric antibody for EGF-r was nearly the same as that of the parental murine antibody. Based on previous in vitro and in vivo animal studies, Mint5 was shown to be a good candidate for the targeting of EGF-r overexpressing tumours. chMint5 is expected to be less immunogenic than murine antibody and therefore, could be useful for human treatment.

L2 ANSWER 12 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:386099 BIOSIS
DN PREV199699108455
TI Clavin, a type-1 ribosome-inactivating protein from Aspergillus clavatus IFO 8605: cDNA isolation, heterologous expression, biochemical and biological characterization of the recombinant protein.
AU Parente, Dino (1); Raucci, Giuseppe; Celano, Bruna; Pacilli, Aurelio; Zanoni, Lorenzo; Canevari, Silvana; Adobati, Elena; Colnaghi, Maria I.; Dosio, Franco; Arpicco, Silvia; Cattel, Luigi; Mele, Antonio; ***De*** *** Santis, Rita***
CS (1) Menarini Ricerche Sud, Biotechnol. Dep., Via Tito Speri 10, I-00040 Pomezia RM Italy
SO European Journal of Biochemistry, (1996) Vol. 239, No. 2, pp. 272-280. ISSN: 0014-2956.
DT Article
LA English
AB We describe the cloning and expression of a new cDNA from the filamentous fungus Aspergillus clavatus IFO 8605. This cDNA contains an open reading frame (ORF) that predicts a putative ribonuclease precursor with high similarity to the alpha-sarcin family of ribosome-inactivating proteins (RIPs). The cDNA encoding the mature protein was expressed in Escherichia

coli, and the recombinant protein, a 17-kDa polypeptide designated clavin was purified and characterized. Clavin shows typical type-1 RIP properties: specific cleavage of ribosomal and synthetic RNA and inhibition of protein synthesis in cell-free and cellular systems. When selectively targeted to a tumour cell antigen by coupling to a monoclonal antibody (mAb) clavin was able to inhibit protein synthesis at nanomolar concentration. Pharmacokinetics analysis in mice indicated an elimination half-life (t-1/2beta) of 7.4 h with no particular accumulation in major organs. Liver toxicity was very limited and transient while no alteration of kidney function was observed. Clavin induced a late and very low antibody response in mice. The in vitro and in vivo biological characteristics of clavin, together with its availability in large amounts, suggest the usefulness of this toxin in the production of toxic chemical conjugates.

L2 ANSWER 13 OF 13 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1996:46592 BIOSIS
DN PREV199698618727
TI Antibody/G-CSF conjugates to stimulate antitumor effect of neutrophilic granulocytes.
AU D'Alatri, Laura (1); Di Loreto, Mario (1); Bullo, Angela (1); Argentino-Storino, Alberta; Manno, Rosa Anna; Venturi, Roberta; De Paolis, Enrico; Pignanelli, Paola (1); ***De Santis, Rita (1)*** ; Mele, Antonio (1); Rotondaro, Luigi (1)
CS (1) Menarini Ricerche Sud, Dep. Biotechnol., Via Tito Speri 10, 00040 Pomezia, Roma Italy
SO Anticancer Research, (1995) Vol. 15, No. 5A, pp. 1837. Meeting Info.: Fifth International Conference of Anticancer Research Corfu, Greece October 17-22, 1995 ISSN: 0250-7005.
DT Conference
LA English

=> d his

(FILE 'HOME' ENTERED AT 14:18:30 ON 11 APR 2002)

FILE 'BIOSIS, MEDLINE, EMBASE' ENTERED AT 14:18:37 ON 11 APR 2002
E DE SANTIS/AU
L1 224 S DE SANTIS R/AU
L2 13 S DE SANTIS RITA/AU

=> s antigen presenting cell? or APC
L3 43464 ANTIGEN PRESENTING CELL? OR APC

=> s hypomethylat? or demethylat? or unmethylat?
L4 27249 HYPOMETHYLAT? OR DEMETHYLAT? OR UNMETHYLAT?

=> s l3 same l4
MISSING OPERATOR L3 SAME
The search profile that was entered contains terms or nested terms that are not separated by a logical operator.

=> s l3 (s) l4
L5 52 L3 (S) L4

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6 24 DUP REM L5 (28 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 24 ANSWERS - CONTINUE? Y/(N):y

L6 ANSWER 1 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
AN 2002:130348 BIOSIS
DN PREV200200130348
TI DNA methylation patterns in hereditary human cancers mimic sporadic tumorigenesis.
AU Esteller, Manel; Fraga, Mario F.; Guo, Mingzhou; Garcia-Foncillas, Jesus; Hedenfalk, Ingrid; Godwin, Andrew K.; Trojan, Joerg; Vaurs-Barriere, Catherine; Bignon, Yves-Jean; Ramus, Susan; Benitez, Javier; Caldes, Trinidad; Akiyama, Yoshimitsu; Yuasa, Yusuhito; Launonen, Virpi; Canal, Maria Jesus; Rodriguez, Roberto; Capella, Gabriel; Peinado, Miguel Angel; Borg, Ake; Aaltonen, Lauri A.; Ponder, Bruce A.; Baylin, Stephen B.; Herman, James G. (1)
CS (1) The Johns Hopkins Oncology Center, 1650 Orleans Street, Room 543, Baltimore, MD, 21231: hermanji@jhmi.edu USA
SO Human Molecular Genetics, (15 December, 2001) Vol. 10, No. 26, pp. 3001-3007. http://hmg.oupjournals.org/?nj. print. ISSN: 0964-6906.
DT Article
LA English
AB Cancer cells have aberrant patterns of DNA methylation including hypermethylation of gene promoter CpG islands and global ***demethylation*** of the genome. Genes that cause familial cancer, as well as other genes, can be silenced by promoter hypermethylation in sporadic tumors, but the methylation of these genes in tumors from kindreds with inherited cancer syndromes has not been well characterized. Here, we examine CpG island methylation of 10 genes (hMLH1, BRCA1, ***APC*** , LKB1, CDH1, p16INK4a, p14ARF, MGMT, GSTP1 and RARbeta2) and 5-methylcytosine DNA content, in inherited (n = 342) and non-inherited (n = 215) breast and colorectal cancers. Our results show that singly retained alleles of germline mutated genes are never hypermethylated in inherited tumors. However, this epigenetic change is a frequent second 'hit', associated with the wild-type copy of these genes in inherited tumors where both alleles are retained. Global ***hypomethylation*** was similar between sporadic and hereditary cases, but distinct differences existed in patterns of methylation at non-familial genes. This study demonstrates the hereditary cancers 'mimic' the DNA methylation patterns present in the sporadic tumors.

L6 ANSWER 2 OF 24 MEDLINE DUPLICATE 2
AN 2001407474 MEDLINE
DN 21341709 PubMed ID: 11448917
TI Aberrant methylation of the adenomatous polyposis coli (APC) gene promoter 1A in breast and lung carcinomas.
AU Virmani A K; Rathi A; Sathyanarayana U G; Padar A; Huang C X; Cunnigham H T; Farinas A J; Milchgrub S; Euhus D M; Gilcrease M; Herman J; Minna J D; Gazdar A F
CS Hamon Center for Therapeutic Oncology Research, and Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas 75390-8593, USA.
NC 4P50CA7097-0452 (NCI) P50CA7097 (NCI)
SO CLINICAL CANCER RESEARCH, (2001 Jul) 7 (7) 1998-2004. Journal code: C2H; 9502500. ISSN: 1078-0432.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200110
ED Entered STN: 20011029 Last Updated on STN: 20011029 Entered Medline: 20011025
AB The adenomatous polyposis coli (***APC***) gene is a tumor suppressor gene associated with both familial and sporadic cancer. Despite high rates of allelic loss in lung and breast cancers, point mutations of the ***APC*** gene are infrequent in these cancer types. Aberrant methylation of the ***APC*** promoter 1A occurs in some colorectal and gastric malignancies, and we investigated whether the same mechanism occurs in lung and breast cancers. The methylation status of the ***APC*** gene promoter 1A was analyzed in 77 breast, 50 small cell (SCLC), and 106 non-small cell (NSCLC) lung cancer tumors and cell lines and in 68 nonmalignant tissues by methylation-specific PCR. Expression of the ***APC*** promoter 1A transcript was examined in a subset of cell lines by reverse transcription-PCR, and loss of heterozygosity at the gene locus was analyzed by the use of 12 microsatellite and polymorphic markers. Statistical tests were two-sided. Promoter 1A was methylated in 34 of 77 breast cancer tumors and cell lines (44%), in 56 of 106 NSCLC tumors and cell lines (53%), in 13 of 50 SCLC cell lines (26%), and in 3 of 68 nonmalignant samples (4%). Most cell lines tested contained the ***unmethylated*** or methylated form exclusively. In 27 cell lines tested, there was complete concordance between promoter methylation and silencing of its transcript. ***Demethylation*** with 5-aza-2'-deoxycytidine treatment restored transcript 1A expression in all eight methylated cell lines tested. Loss of heterozygosity at the ***APC*** locus was observed in 85% of SCLCs, 83% of NSCLCs, and 63% of breast cancer cell lines. The frequency of methylation in breast cancers increased with tumor stage and size. In summary, aberrant methylation of the 1A promoter of the ***APC*** gene and loss of its specific transcript is frequently present in breast and NSCLC cancers and cell lines and, to a lesser extent, in SCLC cell lines. Our findings may be of biological and clinical importance.

L6 ANSWER 3 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2002:157472 BIOSIS
DN PREV200200157472
TI Optimized transfection (nucleofection) of CpG-sequences in immunologic effector cells to increase anti-tumor immunity in adoptive therapy strategies.
AU Gorschlueter, Marcus (1); Schakowski, Frank (1); Schoettker, Bjoern (1); Ziske, Carsten (1); Buttgereit, Peter (1); Schmidt-Wolf, Ingo G. H. (1)
CS (1) Internal Medicine I, University of Bonn, Bonn, NRW Germany
SO Blood, (November 16, 2001) Vol. 98, No. 11 Part 2, pp. 404b. http://www.bloodjournal.org/. print. Meeting Info.: 43rd Annual Meeting of the American Society of Hematology, Part 2 Orlando, Florida, USA December 07-11, 2001 ISSN: 0006-4971.
DT Conference
LA English
AB Bacterial DNA sequences and oligodesoxynucleotides (ODN) containing ***unmethylated*** CpG dinucleotides in a certain base context have the ability to stimulate various immune cells such as ***antigen*** - ***presenting*** ***cells*** , B cells, T cells and NK cells. Therefore, CpG-ODN are promising agents in immunology-based antitumor strategies. Successful use as adjuvants in tumor antigen vaccination or monoclonal antibody therapy has been demonstrated in animal models. CpG-ODN probably elicit their effects by cellular uptake and subsequent

activation of transcription factors in the cytoplasm of immune cells. Surprisingly, the effect of transfection of CpG-ODN on their immunological capabilities has not yet been investigated. We established a CD3+/CD56+ rich cytotoxic effector cell population from peripheral blood of healthy donors. Conditions of CpG-ODN transfection of these cytotoxic T cells which are generally known to be relatively resistant to nonviral gene transfer were optimized. We applied electroporation and various CpG-ODN. Transfection efficiency as assessed by flow cytometry after transfer of fluorescein-labeled CpG-ODN could be increased up to 99% of cytotoxic T cells. The best compromise of transfection efficiency (97.5, +/-1.1%) and toxicity (portion of necrotic cells: 24.5, +/-4.6%) was achieved using 4mug DNA/5* 106 cells, which is a low rate in these vulnerable cells. Proliferation and the proportion of the functional most important CD3+/CD56+ double positive cells was not altered. First results of chromium release assays of transfected cells and colon carcinoma cells as targets showed no significant increase in cytotoxicity. In conclusion, our results show that nucleofection is very efficient in CpG-ODN DNA-transfer in cytotoxic T cells and demonstrate perspectives of this approach for cancer immunotherapy.

L6 ANSWER 4 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
3
AN 2001:83237 BIOSIS
DN PREV200100083237
TI CpG motifs of DNA vaccines induce the expression of chemokines and MHC class II molecules on myocytes.
AU Stan, Alexandru C.; Casares, Sofia; Brumeanu, Teodor-Doru; Klinman, Dennis M.; Bona, Constantin A. (1)
CS (1) Department of Microbiology, Mount Sinai School of Medicine, One Gustave L. Levy Place, New York, NY, 10029-6574: bona@msvax.mssm.edu USA
SO European Journal of Immunology, (January, 2001) Vol. 31, No. 1, pp. 301-310. print.
ISSN: 0014-2980.
DT Article
LA English
SL English
AB Determining how an immune response is initiated after in vivo transfection of myocytes with plasmids encoding foreign antigens is essential to understand the mechanisms of intramuscular (i.m.) genetic immunization. Since myocytes are facultative ***antigen*** - ***presenting*** ***cells*** lacking MHC class II and co-stimulatory molecules, it was assumed that their unique role upon DNA vaccination is to synthesize and secrete the protein encoded by the plasmid. Here we describe that i.m. injection of ***unmethylated*** CpG motifs induced the expression of chemokines (monocyte chemotactic protein-1) and MHC class II molecules on myocytes. Our results indicate that immunostimulatory DNA sequences (CpG motifs) of DNA vaccines augment synthesis of chemokine by myocytes with subsequent recruitment of inflammatory cells secreting IFN-gamma, a potent cytokine that up-regulates the expression of MHC class II molecules on myocytes. A myoblast cell line triple transfected with plasmids encoding MHC class II molecules and an immunodominant CD4 T cell epitope of influenza virus presented the endogenously synthesized peptide and activated specific T cells. These findings suggest that one mechanism for the immunogenicity of DNA vaccines consists in the presentation of peptides to CD4 T cells by in vivo plasmid-transfected myocytes.

L6 ANSWER 5 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
4
AN 2000:483079 BIOSIS
DN PREV200000483079
TI Fields of aberrant CpG island hypermethylation in Barrett's esophagus and associated adenocarcinoma.
AU Eads, Cindy A.; Lord, Reginald V.; Kurumboor, Soudamini K.; Wickramasinghe, Kumari; Skinner, Margaret L.; Long, Tiffany I.; Peters, Jeffrey H.; DeMeester, Tom R.; Danenberg, Kathleen D.; Danenberg, Peter V.; Laird, Peter W. (1); Skinner, Kristin A.
CS (1) Norris Comprehensive Cancer Center, University of Southern California, 1441 Eastlake Avenue, Room 6418, Los Angeles, CA, 90089-9176 USA
SO Cancer Research, (September 15, 2000) Vol. 60, No. 18, pp. 5021-5026. print.
ISSN: 0008-5472.
DT Article
LA English
SL English
AB Esophageal adenocarcinoma (EAC) is thought to develop through a multistage process in which Barrett's metaplasia progresses through low- and high-grade dysplasia to invasive cancer. Transcriptional silencing of tumor suppressor genes by promoter CpG island hypermethylation has been observed in many types of human cancer. Analysis of CpG island hypermethylation in EAC has thus far been limited to the CDKN2A (p16) gene. In this study, we extend the methylation analysis of EAC to include three other genes, ***APC*** , CDH1 (E-cadherin), and ESR1 (ER, estrogen receptor alpha), in addition to CDKN2A. Molecular analysis can provide insight into the complex relationships between tissues with different histologies in Barrett's esophagus and associated adenocarcinoma. Therefore, we have mapped the spatial distribution of methylation patterns in six esophagectomy cases in detail. Hypermethylation of the four CpG islands was analyzed by the MethyLight technique in 107 biopsies derived from these six patients for a total of 428 methylation analyses. Our results show that normal esophageal squamous epithelium is ***unmethylated*** at all four CpG islands. CDH1 is ***unmethylated*** in most other tissue types as well. Hypermethylation of ESR1 is seen at high frequency in inflammatory reflux esophagitis and at all subsequent stages, whereas ***APC*** and CDKN2A hypermethylation is found in Barrett's metaplasia, dysplasia, and EAC. When it occurs, hypermethylation of ***APC*** , CDKN2A, and ESR1 is usually found in a large contiguous field, suggesting either a concerted methylation change associated with metaplasia or a clonal expansion of cells with abnormal hypermethylation.

L6 ANSWER 6 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5
AN 2000:439318 BIOSIS
DN PREV200000439318
TI Distinct methylation patterns of two APC gene promoters in normal and cancerous gastric epithelia.
AU Tsuchiya, Takashi; Tamura, Gen (1); Sato, Kiyoshi; Endoh, Yasushi; Sakata, Ken; Jin, Zhe; Motoyama, Teiichi; Usuba, Osamu; Kimura, Wataru; Nishizuka, Satoshi; Wilson, Keith T.; James, Stephen P.; Yin, Jing; Fleisher, A. Steven; Zou, Tongtong; Silverberg, Steven G.; Kong, Dehe; Meltzer, Stephen J.
CS (1) Department of Pathology, Yamagata University School of Medicine, 2-2-2 Iida-nishi, Yamagata, 990-9585 Japan
SO Oncogene, (July, 2000) Vol. 19, No. 32, pp. 3642-3646. print.
ISSN: 0950-9232.
DT Article
LA English
SL English
AB The adenomatous polyposis coli (***APC***) tumor suppressor gene is mutationally inactivated in both familial and sporadic forms of colorectal cancers. In addition, hypermethylation of CpG islands in the upstream portion of ***APC*** , a potential alternative mechanism of tumor suppressor gene inactivation, has been described in colorectal cancer. Because a subset of both gastric and colorectal cancers display the CpG island methylator phenotype, we hypothesized that epigenetic inactivation of ***APC*** was likely to occur in at least some gastric cancers. ***APC*** exhibits two forms of transcripts from exons 1A and 1B in the stomach. Therefore, we investigated CpG island methylation in the sequences upstream of exons 1A and 1B, i.e., promoters 1A and 1B, respectively. We evaluated DNAs from 10 gastric cancer cell lines, 40 primary gastric cancers, and 40 matching non-cancerous gastric mucosae. Methylated alleles of promoter 1A were present in 10 (100%) of 10 gastric cancer cell lines, 33 (82.5%) of 40 primary gastric cancers, and 39 (97.5%) of 40 non-cancerous gastric mucosae. In contrast, promoter 1B was ***unmethylated*** in all of these same samples. ***APC*** transcripts from exon 1A were not expressed in nine of the 10 methylated gastric cancer cell lines, whereas ***APC*** transcripts were expressed from exon 1B. Thus, expression from a given promoter correlated well with its methylation status. We conclude that in contrast to the colon, methylation of promoter 1A is a normal event in the stomach; moreover, promoter 1B is protected from methylation in the stomach and thus probably does not participate in this form of epigenetic ***APC*** inactivation.

L6 ANSWER 7 OF 24 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2000343036 EMBASE
TI Immunotherapeutic applications of CpG-containing oligodeoxynucleotides.
AU Klinman D.M.; Ishii K.J.; Gursel M.; Gursel I.; Takeshita S.; Takeshita F.
CS Dr. D.M. Klinman, Section of Retroviral Research, Ctr. for Biologics Evaluation/Res., Food and Drug Administration, Bethesda, MD 20892, United States
SO Drug News and Perspectives, (2000) 13/5 (289-296).
Refs: 68
ISSN: 0214-0934 CODEN: DNPEED
CY Spain
DT Journal; General Review
FS 026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Bacterial DNA and synthetic oligodeoxynucleotides (ODN) expressing ***unmethylated*** CpG motifs stimulate the mammalian immune system to mount a rapid innate immune response. This response is characterized by the production of polyreactive IgM, immunomodulatory cytokines and chemokines. CpG ODN directly stimulate lymphocytes, natural killer cells and professional ***antigen*** - ***presenting*** ***cells*** (such as macrophages and dendritic cells). Owing to the strength and nature of this stimulation, CpG ODN are being harnessed for a variety of therapeutic uses. They are being tested for their ability to act as immune adjuvants, boosting the immune response elicited by conventional and DNA vaccines. As a result of their ability to activate a strong interferon gamma-dominated Th1 response while blocking the development of Th2-dependent allergies, CpG ODN are being examined for their antiallergic properties. Finally, CpG ODN are being used as 'immunoprotective agents,' since the innate immune response they elicit can protect the host from a variety of pathogenic bacteria, viruses and parasites. (C) 2000 Prous Science.

L6 ANSWER 8 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:300015 BIOSIS
DN PREV200100300015

TI Up-regulation of CD40 but not CD80 by CPG oligonucleotide treatment of pre-B acute lymphoblastic leukemia cells.
AU Reid, Gregor S. D. (1); Alessandri, Angela J. (1); Grubb, Stacey (1); Bader, Sharon A. (1); Macfarlane, Donald E.; Schultz, Kirk R. (1)
CS (1) Pediatrics, Division of Hematology/Oncology/BMT, University of British Columbia, Vancouver, BC Canada
SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 2, pp. 216b. print
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DT Conference
LA English
SL English
AB Synthetic oligonucleotides (ODNs) containing ***unmethylated*** CpG motifs are stimulatory for B cells and ***antigen*** ***presenting*** ***cells*** . ODN treatment of these cells results in the up-regulation of expression of a variety of accessory molecules, including CD40, CD58, CD80 and CD86. It has recently been shown that incubation of chronic lymphocytic leukemia (CLL) B cells with ODNs resulted in increased proliferation, cytokine production and a more immunogenic phenotype. In this preliminary study we analyzed the effect of ODN treatment on pre-B acute lymphoblastic leukemia (ALL) cells. Using four colour flow cytometry we measured the phenotypic changes on both the normal and leukemic B cells present in patient derived samples. As has been previously reported for B cells from healthy individuals, expression of CD40 and CD80 was increased on normal B cells following incubation with ODNs. In the case of CD10/CD19 positive leukemic blasts, ODN treatment resulted in a large increase in CD40 expression but there was no simultaneous increase in CD80 expression. Addition of soluble trimeric CD40 ligand to ODN treated samples yielded a greater increase in CD40 and CD80 expression on normal B cells than observed with ODN alone. However, the combination failed to significantly augment CD80 expression by pre-B ALL cells, although survival of the leukemia cells was enhanced by this combined treatment. These results indicate that ALL cells respond differently than normal and CLL B cells to ODN treatment and that this approach to increasing immunogenicity may have a more limited application to ALL.

L6 ANSWER 9 OF 24 MEDLINE DUPLICATE 6
AN 2001084160 MEDLINE
DN 20401099 PubMed ID: 10944802
TI Multiple effects of immunostimulatory DNA on T cells and the role of type I interferons.
AU Sun S; Zhang X; Tough D; Sprent J
CS R.W. Johnson Pharmaceutical Research Institute, La Jolla, CA 92121, USA.
NC AI32068 (NIAID)
CA25803 (NCI)
CA38355 (NCI)
+
SO SPRINGER SEMINARS IN IMMUNOPATHOLOGY, (2000) 22 (1-2) 77-84.
Ref: 26
Journal code: VBG. ISSN: 0172-6641.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200101
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010118
AB In addition to stimulating antigen-specific immune responses, infectious agents cause nonspecific activation of the innate immune system, notably up-regulation of costimulatory/adhesion molecules on APCs and cytokine production. In recent years it has become apparent that stimulation of the immune system by microorganisms is a property of a number of different cellular components, including DNA. As discussed earlier and elsewhere in this volume, the DNA of infectious agents--and indeed of all non-vertebrates tested--differs from mammalian DNA in being enriched for ***unmethylated*** CpG motifs. With appropriate flanking sequences, CpG DNA and synthetic CpG ODNs cause strong activation of APCs and other cells. In this article we have focussed on the capacity of CpG DNA/ODNs to alter T cell function. Whether these compounds act directly on T cells or function indirectly by activating other cells, especially APCs, is controversial [7, 8, 13, 14]. In contrast to other workers [8], we have yet to find definitive evidence that CpG DNA/ODNs can provide a co-stimulatory signal for purified T cells subjected to TCR ligation ([14] and unpublished data of authors). For this reason we lean to the notion that CpG DNA/ODNs modulate T cell function by inducing activation of ***APC*** rather than by acting directly on T cells. When injected in vivo in the absence of specific antigen, CpG DNA/ODNs have two striking effects on T cells, namely (1) induction of overt activation (proliferation) of memory-phenotype CD8+ cells, and (2) partial activation of all T cells, including naive-phenotype T cells. Both actions of CpG DNA/ODNs are heavily dependent on the production of IFN-I by ***APC*** . For memory-phenotype (CD44hi) CD8+ cells, neither CpG DNA nor IFN-I can cause proliferation of purified ***APC*** -depleted T cells in vitro. Hence, under in vivo conditions, CpG DNA-induced proliferation of CD44hi CD8+ cells is probably mediated through the production of a secondary cytokine, i.e., by a cytokine that is directly stimulatory for CD44hi CD8+ cells. Based on the available evidence, it is highly likely that the effector cytokine is IL-15. With this assumption, our current model is that proliferation of CD44hi CD8+ cells induced by injection of CpG DNA/ODNs reflects production of IFN-I which, in turn, leads to synthesis of IL-15. Which particular cell types produce these two cytokines is unclear, although APCs are probably of prime importance. In addition to inducing proliferation of memory-phenotype CD8+ cells via IL-15, the IFN-I induced by CpG DNA/ODNs can also induce partial activation of naive T cells. This form of activation leads to up-regulation of CD69 and other molecules but does not cause entry into cell cycle. It is of interest that the partial activation of naive T cells induced by IFN-I is associated with decreased T proliferative responses. Thus, proliferation of purified naive T cells elicited by combined TCR/CD28 ligation in vitro is greatly reduced by addition of IFN-I. This inhibitory effect of IFN-I does not influence cytokine production and probably reflects production of cell cycle inhibitors. Surprisingly, except at high doses, IFN-I fails to exert an anti-proliferative effect when T proliferative responses are driven by viable APCs. Indeed, in this situation, IFN-I enhances antigen-specific T proliferative responses, both in vivo and in vitro. This adjuvant effect of IFN-I is presumably a reflection of ***APC*** activation, but direct evidence on this issue is still lacking. In this article we have emphasized that contact with CpG DNA/ODNs has multiple effects on T cell function in vivo. Many of these effects seem to be related to the production of certain cytokines by APCs, notably IFN-I and IL-15. It should be stressed, however, that CpG DNA/ODNs probably lead to the production of many other cytokines. Hence, our current models of how CpG DNA/ODNs influence T cell function are undoubtedly oversimplified.

L6 ANSWER 10 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
7
AN 2000:116656 BIOSIS
DN PREV200000116656
TI Genetic and environmental factors contributing to the onset of allergic disorders.
AU Parronchi, P.; Brugnolo, F.; Sampognaro, S.; Maggi, E. (1)
CS (1) Dipartimento di Medicina Interna, Sezione di Immunoallergologia e Malattie Respiratorie, Policlinico di Careggi, I-50134, Firenze Italy
SO International Archives of Allergy and Immunology, (Jan., 2000) Vol. 121, No. 1, pp. 2-9.
ISSN: 1018-2438.
DT General Review
LA English
SL English
AB Evidence has been accumulated to suggest that allergen-reactive Th2 cells play a triggering role in the activation and/or recruitment of IgE antibody-producing B cells, mast cells and eosinophils, the cellular triad involved in allergic inflammation. Recently, chemokines and chemokine receptors involved in such Th2-type response have been also defined. Th2 cells represent the polarized arm of the effector-specific responses that contribute to the protection against gastrointestinal nematodes and act as regulatory cells for chronic and/or excessive Th1-mediated responses. Th2 cells are generated from precursor naive Th cells when they encounter the specific antigen in an IL-4-containing microenvironment. The question of how these Th2 cells are selected in atopic patients is also unclear. Both the nature of the T cell receptor signalling provided by the allergen peptide ligand and a disregulation of IL-4 production likely concur to determine the Th2 profile of allergen-specific Th cells, but the genetic unbalanced IL-4 production is certainly overwhelming. Some gene products selectively expressed in Th2 cells or selectively controlling the expression of IL-4 have recently been described. These findings allow to suggest that the upregulation of genes controlling IL-4 expression and/or abnormalities of regulatory mechanisms of Th2 development and/or function may be responsible for Th2 responses against allergens in atopic people. The increasing prevalence of allergy in developed countries suggests that environmental factors acting either before or after birth also contribute to regulate the development of Th2 cells and/or their function. The reduction of infectious diseases in early life due to increasing vaccinations, antimicrobial treatments as well as changed lifestyle are certainly important in influencing the individual outcome in the Th response to ubiquitous allergens. Moreover, the recent evidence that bacterial DNA or oligodeoxynucleotides containing ***unmethylated*** 'CpG motifs' promote the development of Th1 cells via the production of immunomodulatory cytokines (namely IL-12, IL-18 and IFNs) by professional ***antigen*** - ***presenting*** ***cells*** confirms previous epidemiological data. The new insight into the pathophysiology of T cell responses in atopic diseases provides exciting opportunities for the development of novel immunotherapeutic strategies.

L6 ANSWER 11 OF 24 MEDLINE DUPLICATE 8
AN 2000054537 MEDLINE
DN 20054537 PubMed ID: 10586047
TI Bacterial/CpG DNA down-modulates colony stimulating factor-1 receptor surface expression on murine bone marrow-derived macrophages with concomitant growth arrest and factor-independent survival.
AU Sester D P; Beasley S J; Sweet M J; Fowles L F; Cronau S L; Stacey K J; Hume D A
CS Center for Molecular and Cellular Biology, University of Queensland, Australia.
SO JOURNAL OF IMMUNOLOGY, (1999 Dec 15) 163 (12) 6541-50.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Abridged Index Medicus Journals; Priority Journals
EM 200001
ED Entered STN: 20000114
Last Updated on STN: 20000114
Entered Medline: 20000106
AB ***Unmethylated*** CpG motifs within bacterial DNA constitute a pathogen-associated molecular pattern recognized by the innate immune system. Many of the immunomodulatory functions of bacterial DNA can be ascribed to the ability to activate macrophages and dendritic cells. Here we show stimulatory DNA, like LPS, caused growth arrest of murine bone marrow-derived macrophages proliferating in CSF-1. Stimulatory DNA caused selective down-modulation of CSF-1 receptor surface expression. Flow cytometric analysis of CSF-1-deprived bone marrow-derived macrophages revealed that in contrast to the synchronous reduction of CSF-1 receptor upon CSF-1 addition, activating DNA (both bacterial DNA and CpG-containing oligonucleotide) caused rapid removal of receptor from individual cells leading to a bimodal distribution of surface expression at intermediate times or submaximal doses of stimulus. Despite causing growth arrest, both stimulatory DNA and LPS promoted factor-independent survival of bone marrow-derived macrophages, which was associated with phosphorylation of the mitogen-activated protein kinase family members, extracellular-regulated kinase 1 and 2. CSF-1 receptor down-modulation may polarize the professional ***APC*** compartment to the more immunostimulatory dendritic cell-like phenotype by suppressing terminal macrophage differentiation mediated by CSF-1.

L6 ANSWER 12 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
9
AN 2000:76269 BIOSIS
DN PREV200000076269
TI Adjuvant effect of a 14-member macrolide antibiotic on DNA vaccine.
AU Sato, Yukio (1); Shishido, Hideo; Kobayashi, Hiroko; Takeda, Junko; Irisawa, Atsushi; Miyata, Masayuki; Nishimaki, Tomoe; Fujita, Teizo; Kasukawa, Reiji
CS (1) Department of Internal Medicine II, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima, 960-1295 Japan
SO Cellular Immunology, (Nov. 1, 1999) Vol. 197, No. 2, pp. 145-150.
ISSN: 0008-8749.
DT Article
LA English
SL English
AB Macrolide antibiotics have unique immunomodulatory actions apart from their antimicrobial properties. We examined the effect of erythromycin (EM), a 14-member macrolide, on the immune response to a DNA vaccine that induces a T-helper-1 (Th1)-biased immune response through a Th1-promoting adjuvant effect of ***unmethylated*** CpG motifs within plasmid DNA. EM enhanced Th1 responses in plasmid DNA-immunized mice as measured by antigen-specific IgG2a antibody production, interferon-gamma production by antigen-specific CD4+ T cells, and cytotoxic T lymphocyte responses. EM augmented the accessory cell activity of ***unmethylated*** CpG DNA-stimulated ***antigen*** - ***presenting*** ***cells*** (APCs), suggesting that EM enhances Th1 responses to a DNA vaccine, possibly through augmentation of accessory cell activity of APCs stimulated with CpG motifs within plasmid DNA.

L6 ANSWER 13 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
10
AN 1999:212765 BIOSIS
DN PREV199900212765
TI Differentiation of naive human CD4+ T cells into Th2 cells: The role of prostaglandin E2.
AU Katamura, Kenji (1)
CS (1) Department of Pediatrics, Faculty of Medicine, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, Kyoto, 606 Japan
SO Allergology International, (March, 1999) Vol. 48, No. 1, pp. 7-14.
ISSN: 1323-8930.
DT General Review
LA English
SL English
AB T-helper (Th) 2 cells, which produce interleukin (IL)-4, IL-5, IL-10 and IL-13 upon stimulation of their T cell receptors, play an important role in the development of human allergic diseases. However, the precise mechanism involved in the differentiation of Th2 cells is not well understood compared with that of Th1 cells. The selective differentiation of Th1 or Th2 subsets is established during priming under the influence of a variety of factors. Prostaglandin E2 (PGE2) is one of those factors. Prostaglandin E2 produced by ***antigen*** ***presenting*** ***cells*** directly affects the naive CD4+ T cells, causing them to differentiate into Th2 cells. This effect is mediated by the elevation of cyclic adenosine monophosphate (cAMP) at the early stage of T cell activation. IL-4 and PGE2 lead naive CD4+ T cells to differentiate into Th2 cells cooperatively, by distinct signal transduction. Both PGE2 and IL-4 inhibit the ***hypomethylation*** of the proximal regulatory regions of the genomic IFN-gamma gene, whose ***hypomethylation*** has been suggested as being important for the IFN-gamma production by CD4+ T cells stimulated through their antigen receptors. Prostaglandin E2 facilitates Th2 differentiation of naive CD4+ T cells by acting not only on T cells directly but also on ***antigen*** ***presenting*** ***cells*** by inhibiting their IL-12 production. The production of PGE2 by monocytes is increased significantly in allergic patients. These results, taken collectively, suggest that PGE2 plays an important role in facilitating the differentiation of Th2 cells in vivo.

L6 ANSWER 14 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
11
AN 1999:1411 BIOSIS
DN PREV199900001411
TI CpG-DNA-specific activation of antigen-presenting cells requires stress kinase activity and is preceded by non-specific endocytosis and endosomal maturation.
AU Haecker, Hans; Mischak, Harald; Miethke, Thomas; Liptay, Susanne; Schmid, Roland; Sparwasser, Tim; Heeg, Klaus; Lipford, Grayson B.; Wagner, Hermann (1)
CS (1) Inst. Med. Microbiol. Immunol. Hyg., Technische Univ. Muenchen, Trogerstr. 9, D-81675 Munich Germany
SO EMBO (European Molecular Biology Organization) Journal, (Nov. 2, 1998) Vol. 17, No. 21, pp. 6230-6240.
ISSN: 0261-4189.
DT Article
LA English
AB ***Unmethylated*** CpG motifs in bacterial DNA, plasmid DNA and synthetic oligodeoxynucleotides (CpG ODN) activate dendritic cells (DC) and macrophages in a CD40-CD40 ligand-independent fashion. To understand the molecular mechanisms involved we focused on the cellular uptake of CpG ODN, the need for endosomal maturation and the role of the stress kinase pathway. Here we demonstrate that CpG-DNA induces phosphorylation of Jun N-terminal kinase kinase 1 (JNKK1/SEK/MKK4) and subsequent activation of the stress kinases JNK1/2 and p38 in murine macrophages and dendritic cells. This leads to activation of the transcription factor activating protein-1 (AP-1) via phosphorylation of its constituents c-Jun and ATF2. Moreover, stress kinase activation is essential for CpGDNA-induced cytokine release of tumor necrosis factor alpha (TNFalpha) and interleukin-12 (IL-12), as inhibition of p38 results in severe impairment of this biological response. We further demonstrate that cellular uptake via endocytosis and subsequent endosomal maturation is essential for signalling, since competition by non-CpG-DNA or compounds blocking endosomal maturation such as chloroquine or bafilomycin A prevent all aspects of cellular activation. The data suggest that endosomal maturation is required for translation of intraendosomal CpG ODN sequences into signalling via the stress kinase pathway, where p38 kinase activation represents an essential step in CpG-ODN-triggered activation of ***antigen*** - ***presenting*** ***cells*** .

L6 ANSWER 15 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
12
AN 1999:87690 BIOSIS
DN PREV199900087690
TI Type I interferon-mediated stimulation of T cells by CpG DNA.
AU Sun, Siquan; Zhang, Xiaohong; Tough, David F.; Sprent, Jonathan (1)
CS (1) Dep. Immunol., IMM4, Scripps Res. Inst., 10550 N. Torrey Pines Rd., La Jolla, CA 92037 USA
SO Journal of Experimental Medicine, (Dec. 21, 1998) Vol. 188, No. 12, pp. 2335-2342.
ISSN: 0022-1007.
DT Article
LA English
AB Immunostimulatory DNA and oligodeoxynucleotides containing ***unmethylated*** CpG motifs (CpG DNA) are strongly stimulatory for B cells and ***antigen*** - ***presenting*** ***cells*** (APCs). We report here that, as manifested by CD69 and B7-2 upregulation, CpG DNA also induces partial activation of T cells, including naive-phenotype T cells, both in vivo and in vitro. Under in vitro conditions, CpG DNA caused activation of T cells in spleen cell suspensions but failed to stimulate highly purified T cells unless these cells were supplemented with APCs. Three lines of evidence suggested that ***APC*** -dependent stimulation of T cells by CpG DNA was mediated by type I interferons (IFN-I). First, T cell activation by CpG DNA was undetectable in IFNIR-/- mice. Second, in contrast to normal T cells, the failure of purified IFN-IR-/- T cells to respond to CpG DNA could not be overcome by adding normal IFN-IR+ APCs. Third, IFN-I (but not IFN-gamma) caused the same pattern of partial T cell activation as CpG DNA. Significantly, T cell activation by IFN-I was ***APC*** independent. Thus, CpG DNA appeared to stimulate T cells by inducing APCs to synthesize IFN-1, which then acted directly on T cells via IFN-IR. Functional studies suggested that activation of T cells by IFN-I was inhibitory. Thus, exposing normal (but not IFN-IR-/-) T cells to CpG DNA in vivo led to reduced T proliferative responses after TCR ligation in vitro.

L6 ANSWER 16 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
13
AN 1998:228831 BIOSIS
DN PREV199800228831
TI DNA as an adjuvant: Capacity of insect DNA and synthetic oligodeoxynucleotides to augment T cell responses to specific antigen.
AU Sun, Siquan; Kishimoto, Hidehiro; Sprent, Jonathan (1)
CS (1) Dep. Immunol., IMM4, Scripps Res. Inst., 10550 North Torrey Pines Rd., La Jolla, CA 92037 USA
SO Journal of Experimental Medicine, (April 6, 1998) Vol. 187, No. 7, pp. 1145-1150.
ISSN: 0022-1007.
DT Article

LA English
AB How strong adjuvants such as complete Freund's adjuvant (CFA) promote T cell priming to protein antigens in vivo is still unclear. Since the ***unmethylated*** CpG motifs in DNA of bacteria and other nonvertebrates are stimulatory for B cells and ***antigen*** - ***presenting*** ***cells*** , the strong adjuvanticity of CFA could be attributed, at least in part, to the presence of dead bacteria, i.e., a source of stimulatory DNA. In support of this possibility, evidence is presented that insect DNA in mineral oil has even stronger adjuvant activity than CFA by a number of parameters. Synthetic oligodeoxynucleotides (ODNs) containing ***unmethylated*** CpG motifs mimic the effects of insect DNA and, even in soluble form, ODNs markedly potentiate clonal expansion of T cell receptor transgenic T cells responding to specific peptide.

L6 ANSWER 17 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
14
AN 1998:78403 BIOSIS
DN PREV199800078403
TI Immunostimulatory DNA: Sequence-dependent production of potentially harmful or useful cytokines.
AU Lipford, Grayson B.; Sparwasser, Tim; Bauer, Marc; Zimmermann, Stefan; Koch, Eva-Sophie; Heeg, Klaus; Wagner, Hermann (1)
CS (1) Inst. Med. Microbiol. Immunol. Hyg., Trogerstr. 9, D-81675 Munich Germany
SO European Journal of Immunology, (Dec., 1997) Vol. 27, No. 12, pp. 3420-3426.
ISSN: 0014-2980.
DT Article
LA English
AB Certain bacterial immunostimulatory (i.s.) DNA sequences containing ***unmethylated*** CpG motifs stimulate ***antigen*** - ***presenting*** ***cells*** (***APC***) to express a full complement of costimulatory molecules and to produce cytokines including interleukin (IL)-12 and tumor necrosis factor (TNF)-alpha. While IL-12 is key to their T helper cell (Th)1 -promoting adjuvant activity, secretion of toxic levels of TNF-alpha is harmful in that it promotes toxic shock. Given the beneficial as well as harmful consequences of i.s. DNA, we investigated the possibility of identifying DNA sequences, i.e. CpG oligodeoxynucleotides (ODN) which differentially activate IL-12 versus TNF-alpha cytokine production in ***APC*** . Here, we describe an i.s. DNA sequence with these characteristics. While its potential to induce IL-12 is preserved, its ability to trigger TNF-alpha release is strongly curtailed both in vitro and in vivo. I.s. DNA could be segregated into lethal and non-lethal in a mouse toxic shock model. The non-toxic i.s. DNA was useful as an adjuvant, thus allowing cytotoxic T cell responses to the soluble protein ovalbumin and conferring a resistant Th 1 phenotype to BALB/c mice lethally infected with Leishmania major. This i.s. CpG motif may thus be prototypic for a useful immunostimulating DNA sequence that lacks harmful side effects.

L6 ANSWER 18 OF 24 MEDLINE
AN 1998100967 MEDLINE
DN 98100967 PubMed ID: 9438104
TI Molecular biology of colorectal cancer.
AU Gryfe R; Swallow C; Bapat B; Redston M; Gallinger S; Couture J
CS Department of Surgery, University of Toronto, Ontario, Canada.
SO CURRENT PROBLEMS IN CANCER, (1997 Sep-Oct) 21 (5) 233-300. Ref: 327
Journal code: DU8; 7702986. ISSN: 0147-0272.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199802
ED Entered STN: 19980226
Last Updated on STN: 19980226
Entered Medline: 19980219
AB Colorectal cancer is a significant cause of morbidity and mortality in Western populations. This cancer develops as a result of the pathologic transformation of normal colonic epithelium to an adenomatous polyp and ultimately an invasive cancer. The multistep progression requires years and possibly decades and is accompanied by a number of recently characterized genetic alterations. Mutations in two classes of genes, tumor-suppressor genes and proto-oncogenes, are thought to impart a proliferative advantage to cells and contribute to development of the malignant phenotype. Inactivating mutations of both copies (alleles) of the adenomatous polyposis coli (***APC***) gene--a tumor-suppressor gene on chromosome 5q--mark one of the earliest events in colorectal carcinogenesis. Germline mutation of the ***APC*** gene and subsequent somatic mutation of the second ***APC*** allele cause the inherited familial adenomatous polyposis syndrome. This syndrome is characterized by the presence of hundreds to thousands of colonic adenomatous polyps. If these polyps are left untreated, colorectal cancer develops. Mutation leading to dysregulation of the K-ras protooncogene is also thought to be an early event in colon cancer formation. Conversely, loss of heterozygosity on the long arm of chromosome 18 (18q) occurs later in the sequence of development from adenoma to carcinoma, and this mutation may predict poor prognosis. Loss of the 18q region is thought to contribute to inactivation of the DCC tumor-suppressor gene. More recent evidence suggests that other tumor-suppressor genes--DPC4 and MADR2 of the transforming growth factor beta (TGF-beta) pathway--also may be inactivated by allelic loss on chromosome 18q. In addition, mutation of the tumor-suppressor gene p53 on chromosome 17p appears to be a late phenomenon in colorectal carcinogenesis. This mutation may allow the growing tumor with multiple genetic alterations to evade cell cycle arrest and apoptosis. Neoplastic progression is probably accompanied by additional, undiscovered genetic events, which are indicated by allelic loss on chromosomes 1q, 4p, 6p, 8p, 9q, and 22q in 25% to 50% of colorectal cancers. Recently, a third class of genes, DNA repair genes, has been implicated in tumorigenesis of colorectal cancer. Study findings suggest that DNA mismatch repair deficiency, due to germline mutation of the hMSH2, hMLH1, hPMS1, or hPMS2 genes, contributes to development of hereditary nonpolyposis colorectal cancer. The majority of tumors in patients with this disease and 10% to 15% of sporadic colon cancers display microsatellite instability, also know as the replication error positive (RER+) phenotype. This molecular marker of DNA mismatch repair deficiency may predict improved patient survival. Mismatch repair deficiency is thought to lead to mutation and inactivation of the genes for type II TGF-beta receptor and insulin-like growth-factor II receptor. Individuals from families at high risk for colorectal cancer (hereditary nonpolyposis colorectal cancer or familial adenomatous polyposis) should be offered genetic counseling, predictive molecular testing, and when indicated, endoscopic surveillance at appropriate intervals. Recent studies have examined colorectal carcinogenesis in the light of other genetic processes. Telomerase activity is present in almost all cancers, including colorectal cancer, but rarely in benign lesions such as adenomatous polyps or normal tissues. Furthermore, genetic alterations that allow transformed colorectal epithelial cells to escape cell cycle arrest or apoptosis also have been recognized. In addition, ***hypomethylation*** or hypermethylation of DNA sequences may alter gene expression without nucleic acid mutation.

L6 ANSWER 19 OF 24 MEDLINE
AN 97054072 MEDLINE
DN 97054072 PubMed ID: 8898451
TI Genetic aspects of colorectal cancer: the surgeon's view.
AU Sjodahl R; Nystrom P O
CS Dept. of Surgery, University Hospital, Linkoping, Sweden.
SO SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY. SUPPLEMENT, (1996) 220 132-6.
Ref: 15
Journal code: UCT; 0437034. ISSN: 0085-5928.
CY Norway
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199701
ED Entered STN: 19970219
Last Updated on STN: 19970219
Entered Medline: 19970121
AB A characteristic feature of colorectal cancer genesis is its stepwise progression, which offers unique possibilities for studying its development. There are two principal kinds of mutation leading to uncontrolled cell proliferation and cancer. The first renders a stimulatory gene hyperactive--generation of an oncogene--and the second is the inactivation of a tumour suppressor gene. Current knowledge suggest that the change from normal mucosa to a small adenoma may be mediated by mutations of the ***APC*** gene and MCC gene on chromosome 5, by chromosome 5 deletion, by c-myc activation, and by DNA ***hypomethylation*** . The development to a large adenoma may be caused by Ki-ras mutation and further change to a dysplastic adenoma by deletion of the DCC gene on chromosome 18. The ability to become an invasive carcinoma may then be mediated by p53 mutations and deletion of chromosome 17p. Identification of genetic markers for metastatic disease is under progress.

L6 ANSWER 20 OF 24 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 96310923 EMBASE
DN 1996310923
TI Genetic aspects of colorectal cancer: The surgeon's view.
AU Sjodahl R.; Nystrom P.O.
CS Department of Surgery, University Hospital,581 85 Linkoping, Sweden
SO Scandinavian Journal of Gastroenterology, Supplement, (1996) 31/220 (132-136).
ISSN: 0085-5928 CODEN: SJGSB8
CY Norway
DT Journal; Conference Article
FS 016 Cancer
022 Human Genetics
048 Gastroenterology
LA English
SL English
AB A characteristic feature of colorectal cancer genesis is its stepwise progression, which offers unique possibilities for studying its development. There are two principal kinds of mutation leading to uncontrolled cell proliferation and cancer. The first renders a stimulatory gene hyperactive - generation of an oncogene - and the second is the inactivation of a tumour suppressor gene. Current knowledge suggests that the change from normal mucosa to a small adenoma may be mediated by mutations of the ***APC*** gene and MCC gene on chromosome

5, by chromosome 5 deletion, by c-myc activation, and by DNA ***hypomethylation*** . The development to a large adenoma may be caused by Ki-ras mutations and further change to a dysplastic adenoma by deletion of the DCC gene on chromosome 18. The ability to become an invasive carcinoma may then be mediated by p53 mutations and deletion of chromosome 17p. Identification of genetic markers for metastatic disease is under progress.

L6 ANSWER 21 OF 24 MEDLINE
AN 96287010 MEDLINE
DN 96287010 PubMed ID: 8697090
TI Multiple gene alterations involved in the processor of human gastric carcinogenesis.
AU Lu Y; Li Z; Sun M
CS School of Oncology, Beijing Medical University.
SO CHUNG-HUA I HSUEH TSA CHIH [CHINESE MEDICAL JOURNAL], (1995 Nov) 75 (11) 679-82, 710-1.
Journal code: CDG; 7511141. ISSN: 0376-2491.
CY China
DT Journal; Article; (JOURNAL ARTICLE)
LA Chinese
FS Priority Journals
EM 199609
ED Entered STN: 19960912
Last Updated on STN: 19960912
Entered Medline: 19960903
AB The investigation of molecular evidence of gastric carcinoma will be contributable to the prevention, gene diagnosis and therapy of human gastric neoplasms. To determine the specific genetic change in human gastric cancer (HGC) and precancerous lesions, we analysized FISH, PCR/SSCP, IHC and DNA sequencing by using multiple probes to detect the gene abnormalities (mutation, deletion, amplification or overexpression of genes) of 67 fresh tumors, 63 endoscopic biopsies including 30 dysplasia (DYS) and 33 intestinal metaplasia (IM, and 4 tumor cell lines from HGC patients. Multiple genetic abnormalities including ***hypomethylation*** of H-ras gene, amplification and overexpression of met and erbB2, deletion of ***APC*** , mts1/p16, p53 and nm23 gene and point mutation of p53 gene were noted in HGC and precancerous lesion of human gastric mucosa. Among these changes, p53 gene was the highest frequence genetic alteration in 39/67 (54-58%) of gastric carcinoma. These results indicate that overexpression of met and H-ras occurs at early stage in progression of neoplasia, amplification of met, erbB2 and akt2 gene occurs at progressing stage of tumorigenesis, deletion of p53, ***APC*** , mts1/p16 and nm23 occurs at advanced stage in the progression of cancer. The abnormalities should be associated with malignant phenotypes: poor differentiation, vascular invasion, lymph nodes metastasis, and low survival time. We detected p53 gene mutation in both cancer and precancerous lesions of IM and DYS. These results suggest that p53 may be a susceptible gene and alteration of p53 gene plays an important role in the development of HGC.

L6 ANSWER 22 OF 24 MEDLINE DUPLICATE 15
AN 96351364 MEDLINE
DN 96351364 PubMed ID: 8718526
TI Emergent issues in the genetics of intestinal neoplasia.
AU Dove W F; Gould K A; Luongo C; Moser A R; Shoemaker A R
CS McArdle Laboratory for Cancer Research, University of Wisconsin, Madison 53706, USA.
NC CA07075 (NCI)
CA23076 (NCI)
CA50585 (NCI)
+
SO CANCER SURVEYS, (1995) 25 335-55. Ref: 98
Journal code: CNG; 8218015. ISSN: 0261-2429.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS Priority Journals
EM 199610
ED Entered STN: 19961025
Last Updated on STN: 19961025
Entered Medline: 19961011
AB Mutation of the ***APC*** gene may be a common denominator of all human colon cancer--polypoid and non-polypoid familial cancer as well as sporadic occurrences. Fearon and Vogelstein (1990) have described a series of molecular changes during the progression of human colon cancer, beginning with mutations in ***APC*** . Min is a strain of the laboratory mouse carrying a nonsense mutation in ***Apc*** , the mouse homologue of ***APC*** . The Min strain has been used to test the effect of germline alterations in certain genes identified in the progression pathway of Fearon and Vogelstein. A deficiency in DNA cytosine methylase leads to a reduction in the tumour multiplicity of Min mice contrary to the a priori expectation based on the global ***hypomethylation*** of the DNA of early colonic neoplasms. Alterations in Kras had no perceptible effect on the tumour multiplicity of Min mice but may not have been successfully directed to the proliferative cell population. Constitutional mutation of p53 did not influence the multiplicity or histopathology of early Min induced intestinal tumours. The cause and effect analysis of the genetics of colon cancer is clearly in an early phase. An unlinked genetic factor interacting with Min in controlling intestinal tumour multiplicity is Mom1. A central goal for the near future is to identify the Mom1 gene product and to identify other loci that can interact with the Min mutation and affect tumour multiplicity or progression. Mouse chimaeras will permit an analysis of the clonality and cell autonomy of Min induced neoplasms and also of the action of Mom1. The results of these analyses will inform investigators as to what modes of prevention and therapy might be designed for particular tumour types. The Min strain thereby presents an opportunity to discover protective factors against human colon cancer.

L6 ANSWER 23 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
16
AN 1995:300991 BIOSIS
DN PREV199598315291
TI Suppression of intestinal neoplasia by DNA hypomethylation.
AU Laird, Peter W. (1); Jackson-Grusby, Laurie (1); Fazeli, Amin (1); Dickinson, Stephanie L. (1); Jung, W. Edward (1); Li, En; Weinberg, Robert A. (1); Jaenisch, Rudolf (1)
CS (1) Whitehead Inst. Biomed. Research, Dep. Biol., Massachusetts Inst. Technol., Cambridge, MA 02142 USA
SO Cell, (1995) Vol. 81, No. 2, pp. 197-205.
ISSN: 0092-8674.
DT Article
LA English
AB We have used a combination of genetics and pharmacology to assess the effects of reduced DNA methyltransferase activity on ***Apc*** -Min-induced intestinal neoplasia in mice. A reduction in the DNA methyltransferase activity in Min mice due to heterozygosity of the DNA methyltransferase gene, in conjunction with a weekly dose of the DNA methyltransferase inhibitor 5-aza-deoxycytidine, reduced the average number of intestinal adenomas from 113 in the control mice to only 2 polyps in the treated heterozygotes. Hence, DNA methyltransferase activity contributes substantially to tumor development in this mouse model of intestinal neoplasia. Our results argue against an oncogenic effect of DNA ***hypomethylation*** . Moreover, they are consistent with a role for DNA methyltransferase in the generation of the C to T transitions seen at high frequency in human colorectal tumors.

L6 ANSWER 24 OF 24 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
17
AN 1990:332161 BIOSIS
DN BA90:40180
TI CD4-POSITIVE CELLS TREATED WITH DNA METHYLATION INHIBITORS INDUCE
AUTOLOGOUS B CELL DIFFERENTIATION.
AU RICHARDSON B C; LIEBLING M R; HUDSON J L
CS UNIV. MICHIGAN, ANN ARBOR, MICHIGAN 48109-0531.
SO CLIN IMMUNOL IMMUNOPATHOL, (1990) 55 (3), 368-381.
CODEN: CLIIAT. ISSN: 0090-1229.
FS BA; OLD
LA English
AB The DNA methylation inhibitor 5-azacytidine induces autoreactivity in cloned CD4+ T cells, but the functional consequences of this response are unknown. We now report that CD4+ T cells treated with 5-azacytidine respond to autologous ***antigen*** - ***presenting*** ***cells*** and induce autologous B cell differentiation without exogenous antigen or mitogen. This mechanism could play a role in some autoimmune diseases characterized by T cell DNA ***hypomethylation*** and polyclonal B cell activation.

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=> d his

(FILE 'HOME' ENTERED AT 14:18:30 ON 11 APR 2002)

FILE 'BIOSIS, MEDLINE, EMBASE' ENTERED AT 14:18:37 ON 11 APR 2002
E DE SANTIS/AU
L1 224 S DE SANTIS R/AU
L2 13 S DE SANTIS RITA/AU
L3 43464 S ANTIGEN PRESENTING CELL? OR APC
L4 27249 S HYPOMETHYLAT? OR DEMETHYLAT? OR UNMETHYLAT?
L5 52 S L3 (S) L4
L6 24 DUP REM L5 (28 DUPLICATES REMOVED)

=> s cancer testis antigen? or CTA
L7 3494 CANCER TESTIS ANTIGEN? OR CTA

=> s l7 and review
L8 94 L7 AND REVIEW

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9 64 DUP REM L8 (30 DUPLICATES REMOVED)

=> d bib abs 1-10

L9 ANSWER 1 OF 64 MEDLINE
AN 2002202428 IN-PROCESS
DN 21932993 PubMed ID: 11935044
TI CT angiography with whole brain perfused blood volume imaging: added clinical value in the assessment of acute stroke.

AU Ezzeddine Mustapha A; Lev Michael H; McDonald Colin T; Rordorf Guy; Oliveira-Filho Jamary; Aksoy Fatma Gul; Farkas Jeffrey; Segal Alan Z; Schwamm Lee H; Gonzalez R Gilberto; Koroshetz Walter J
CS Stroke Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Md, USA.
NC NS-34626 (NINDS)
RR-13213 (NCRR)
SO STROKE, (2002 Apr) 33 (4) 959-66.
Journal code: 0235266. ISSN: 1524-4628.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20020406
Last Updated on STN: 20020406
AB BACKGROUND AND PURPOSE: In CT angiographic and perfusion imaging (***CTA*** /CTP), rapid CT scanning is performed during the brief steady state administration of a contrast bolus, creating both vascular phase images of the major intracranial vessels and perfused blood volume-weighted parenchymal phase images of the entire brain. We assessed the added clinical value of the data provided by ***CTA*** /CTP over that of clinical examination and noncontrast CT (NCCT) alone. METHODS: NCCT and ***CTA*** /CTP imaging was performed in 40 patients presenting with an acute stroke. Short clinical vignettes were retrospectively prepared. After concurrent ***review*** of the vignettes and NCCT, a stroke neurologist rated infarct location, vascular territory, vessel(s) occluded, and Trial of Org 10172 in Acute Stroke Treatment (TOAST) and Oxfordshire Community Stroke Project classifications. The ratings were repeated after serial ***review*** of each of the ***CTA*** /CTP components: (1) axial ***CTA*** source images; (2) CTP whole brain blood volume-weighted source images; and (3) maximum-intensity projection 3-dimensional reformatted images. The sequential ratings for each case were compared with the final discharge assessment. RESULTS: Compared with the initial ***review*** after NCCT, ***CTA*** /CTP improved the overall accuracy of infarct localization (P<0.001), vascular territory determination (P=0.003), vessel occlusion identification (P<0.001), TOAST classification (P=0.039), and Oxfordshire Community Stroke Project classification (P<0.001) by 40%, 28%, 38%, 18%, and 32%, respectively. CONCLUSIONS: Admission ***CTA*** /CTP imaging significantly improves accuracy, over that of initial clinical assessment and NCCT imaging alone, in the determination of infarct localization, site of vascular occlusion, and Oxfordshire classification in acute stroke patients.

L9 ANSWER 2 OF 64 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2002093017 EMBASE
TI ***Cancer*** / ***testis*** ***antigens*** : Structural and immunobiological properties.
AU Kirkin A.F.; Dzhandzhugazyan K.N.; Zeuthen J.
CS Dr. J. Zeuthen, Department of Tumor Cell Biology, Institute of Cancer Biology, Danish Cancer Society, Strandboulevarden 49, DK-2100 Copenhagen, Denmark. jz@cancer.dk
SO Cancer Investigation, (2002) 20/2 (222-236).
Refs: 106
ISSN: 0735-7907 CODEN: CINVD7
CY United States
DT Journal; General Review
FS 016 Cancer
026 Immunology, Serology and Transplantation
028 Urology and Nephrology
LA English
SL English
AB Characterization of tumor-associated antigens recognized by cytotoxic T lymphocytes which has evolved during recent years opens new possibilities for specific anti-cancer immunotherapy. Among different groups of tumor-associated antigens, cancer/testis (CT) antigens (expressed in many tumors and among normal tissues only in testes) represent the most perspective antigens for immunotherapy because of their broad tumor-specific expression. More than 50 CT antigens have been described so far and, for many of them, epitopes recognized by T lymphocytes have been identified. The most studied group of CT antigens is the MAGE proteins, which form the so-called MAGE superfamily, together with some MAGE-like proteins that have a different distribution than classical CT antigens. The MAGE superfamily includes five families: MAGE-A, MAGE-B, MAGE-C, MAGE-D, and necdin. Comparison of the structure of members of MAGE superfamily points to the existence of a domain organization of these proteins. The central, core domain (second domain) is highly conservative. The first domain is homologous among MAGE family members with a CT expression, but unique for each member of the MAGE-D and necdin families. In addition to the homology of the central domain, the third domain is also homologous among all members of MAGE superfamily, but to a much lesser extent. The MAGE-D proteins contain an additional, fourth domain, which in the case of MAGE-D3 coincides with trophinin, a separate molecule described previously as an adhesion molecule that participates in embryo implantation. The structural classification of the members of MAGE superfamily might help in the future to understand the biological function of MAGE proteins. One important property of the CT antigens is the up-regulation of their expression by DNA demethylating agents, indicating a possible mechanism for their reexpression in tumors. One of the implications of this particular property could be that a combination of immunotherapy targeting CT antigens with chemotherapy inducing up-regulation of CT antigens might result in more efficient tumor eradication.

L9 ANSWER 3 OF 64 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2001165190 EMBASE
TI [Spiral computer tomographic angiography as a substitute for intra-arterial angiography of the aorta and its branches].
SPIRAALTOMOGRAFISCHE ANGIOGRAFIE ALS VERVANGER VAN INTRA-ARTERIELE
ANGIOGRAFIE VAN AORTA EN ZIJTAKKEN.
AU Wever J.J.; Blankensteijn J.D.; Eikelboom B.C.; Mali W.P.Th.M.
CS Dr. J.D. Blankensteijn, Academisch Ziekenhuis, Afd. Vaatchirurgie, Postbus 85.500, 3508 GA Utrecht, Netherlands. j.d.blankensteijn@chir.azu.nl
SO Nederlands Tijdschrift voor Geneeskunde, (5 May 2001) 145/18 (858-866).
Refs: 33
ISSN: 0028-2162 CODEN: NETJAN
CY Netherlands
DT Journal; General Review
FS 008 Neurology and Neurosurgery
014 Radiology
LA Dutch
SL English; Dutch
AB Until recently, intra-arterial angiography was the diagnostic method of first choice when pathology of the aorta or its branches was suspected. A disadvantage of this technique is that only the lumen of spaces with blood flow can be visualised and that the soft tissue surroundings remain (partly) invisible. - Spiral computer tomographic angiography (***CTA***) has some major advantages compared with conventional angiography. The technique is less invasive and faster. Also, the soft tissue is imaged by ***CTA*** . In addition, computer reconstructions allow viewing from all directions without the limitations of overprojection. - Spiral ***CTA*** is a suitable technique for imaging the thoracic part of the aorta: in case of dissection if transoesophageal echography is not available, in case of an aneurysm to determine the diameter and in case of rupture as a highly sensitive but not very specific examination technique. - For imaging of the abdominal part of the aorta, spiral ***CTA*** may be considered. In case of an aneurysm or a possible rupture of this part of the aorta it is then possible to visualize the operation area and to choose the optimal approach. - For the exclusion of stenoses in mesenteric arteries or in renal arteries, spiral ***CTA*** offers the advantage of non-invasivity. The technique is less suitable for demonstration of these stenoses and does not allow immediate intervention.

L9 ANSWER 4 OF 64 MEDLINE DUPLICATE 1
AN 2001502480 MEDLINE
DN 21436676 PubMed ID: 11552378
TI [Modern diagnostic concepts in dissection and aortic occlusion].
Moderne Diagnostikkonzepte bei Dissektion und Aortenverschluss.
AU Vogt F M; Goyen M; Debatin J F
CS Zentralinstitut fur Rontgendiagnostik, Universitatsklinikum Essen, Hufelandstrasse 55, 45122 Essen.. florian.vogt@uni-essen.de
SO RADIOLOGE, (2001 Aug) 41 (8) 640-52.
Journal code: 0401257. ISSN: 0033-832X.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA German
FS Priority Journals
EM 200112
ED Entered STN: 20010913
Last Updated on STN: 20020122
Entered Medline: 20011204
AB For the diagnostic work-up of the aorta, non-invasive cross-sectional imaging techniques have almost replaced invasive catheter angiography. CT- and MR-angiography are supplemented by sonography which is used predominantly for the assessment of abdominal aortic aneurysm and dissections of the thoracic aorta. This ***review*** deals with the diagnostic approach to two disease entities involving the aorta: aortic dissection and aortic occlusion. Transoesophageal echocardiography (TEE), CT- and MR-angiography (MRA) are used in the assessment of aortic dissection. Published sensitivity and specificity values regarding the detection and classification of dissections into Stanford A and Stanford B range between 96-100% for all three modalities. Results for multislice ***CTA*** have not yet been reported, but can be expected to be at least as good. The ability to delineate additional information regarding the precise morphology of true and false lumen, entry and reentry-sites, the development of thrombus or paraaortic hematomas, as well as the assessment of aortic regurgitation or involvement of coronary arteries depend on the chosen technique. Reflecting the ability to collect functional imaging data, both TEE and MRA are superior to ***CTA*** in the assessment of aortic valve involvement, while TEE is the modality of choice for evaluation of coronary arteries. Sonography is of limited use in the assessment of abdominal dissections. For the evaluation of patients with suspected aortic occlusion both ***CTA*** and MRA represent the imaging modalities of choice. Both provide for a comprehensive and precise depiction of the underlying aortic morphology, the extent of collateral flow as well as delineation of distal run-off vessels. MRA should be employed in patients with impaired renal function as paramagnetic contrast agents are not nephrotoxic.

L9 ANSWER 5 OF 64 MEDLINE DUPLICATE 2
AN 2001424436 MEDLINE
DN 21365882 PubMed ID: 11473192
TI Three-dimensional volume-rendering CT angiography in vasculitis: spectrum of disease and clinical utility.
AU Scatarige J C; Urban B A; Hellmann D B; Fishman E K

CS Russell H. Morgan Department of Radiology and Radiological Sciences, Johns
Hopkins Medical Institutions, Baltimore, MD 21287, USA.
SO JOURNAL OF COMPUTER ASSISTED TOMOGRAPHY, (2001 Jul-Aug) 25 (4) 598-603.
Journal code: HVT; 7703942. ISSN: 0363-8715.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809
AB Spiral computed tomographic angiography (***CTA***) coupled with three-dimensional volume-rendering image processing is a less invasive alternative to conventional catheter angiography. The technique has been used successfully in a variety of vascular diseases. In this pictorial essay, we ***review*** the ***CTA*** findings in selected cases of vasculitis. Technical considerations and the potential clinical value of this method are discussed.

L9 ANSWER 6 OF 64 MEDLINE DUPLICATE 3
AN 2001424430 MEDLINE
DN 21365876 PubMed ID: 11473186
TI CT findings following the cabrol composite graft procedure.
AU Hagspiel K D; Spinosa D J; Angle J F; Matsumoto A H; Leung D A; Spellman M
J Jr; King R C; Kron I L
CS Department of Radiology, University of Virginia Health System, Charlottesville, VA 22908, USA.. kdh2n@virginia.edu
SO JOURNAL OF COMPUTER ASSISTED TOMOGRAPHY, (2001 Jul-Aug) 25 (4) 563-8.
Journal code: HVT; 7703942. ISSN: 0363-8715.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200108
ED Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809
AB PURPOSE: Insertion of a composite graft and reimplantation of the coronary arteries through an intermediate Dacron tube (Cabrol composite graft procedure) has been used to treat ascending aortic aneurysms and dissections. The CT findings after the Cabrol composite graft procedure have not been previously described. METHOD: Retrospective ***review*** of 12 postoperative CT and CT angiography (***CTA***) studies both in the immediate postoperative period as well as during long-term follow-up was conducted. RESULTS: The Cabrol composite graft procedure produces typical CT findings consisting of a coronary conduit separate from the aortic graft. The presence of perigraft flow can be normal or abnormal depending on the time point of its occurrence and the extent of its hemodynamic consequences. CONCLUSION: Knowledge of the typical CT and ***CTA*** findings following a Cabrol composite graft procedure is essential for the correct interpretation of these studies.

L9 ANSWER 7 OF 64 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2001309218 EMBASE
TI Endoluminal treatment of abdominal aortic aneurysms.
AU Vignali C.; Cioni R.; Neri E.; Petruzzi P.; Bargellini I.; Sardella S.; Ferrari M.; Caramella D.; Bartolozzi C.
CS C. Vignali, Division of Diagnostic, Department of Oncology, University of Pisa, Via Roma 67, 56127 Pisa, Italy
SO Abdominal Imaging, (2001) 26/5 (461-468).
Refs: 70
ISSN: 0942-8925 CODEN: ABIMEL
CY United States
DT Journal; General Review
FS 009 Surgery
014 Radiology
LA English
SL English
AB Background: We report our preliminary results with endovascular treatment of abdominal aortic aneurysms (AAA). Methods: Between October 1998 and June 2000, 64 patients (62 male, two female; mean age = 70 years) underwent endovascular repair of AAA. Different types of prostheses were used, both bifurcated (n = 58) and straight (n = 6). We performed duplex sonography and spiral computed tomographic angiography (***CTA***) at discharge and at 3, 6, 12, and 18 months. Follow-up ranged from 1 to 20 months. Results: All procedures were successful, except for three immediate and one late surgical conversions (6.2%). One patient died 14 days after immediate surgical conversion. At discharge, ***CTA*** showed 13 endoleaks: three resolved spontaneously, six persisted during follow-up, and four (one angioplasty and three embolizations) were treated successfully. Stenosis of an iliac branch occurred in one patient after 3 months and was successfully treated by angioplasty. Late endoleaks were detected by imaging follow-up in four cases, three at 1 year and one at 6 months, requiring deployment of distal extender cuffs (n = 2), a proximal cuff (n = 1), and lumbar embolization (n = 2). Conclusion: Our preliminary experience supports the efficacy of endovascular repair in selected patients, but strict and accurate follow-up is required.

L9 ANSWER 8 OF 64 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
4
AN 2002:207874 BIOSIS
DN PREV200200207874
TI Intermediate probability lung scans (IPLS): Retrospective ***review*** of 82 cases.
AU Wong, W. Y. (1); Ng, D. C. E.; Ang, E. S.; Goh, A. S. W.; Sundram, F. X.
CS (1) Department of Nuclear Medicine, Singapore General Hospital, Outram Road, Block 2 Basement 1, Singapore, 169608 Singapore
SO SMJ Singapore Medical Journal, (October, 2001) Vol. 42, No. 10, pp. 450-454. print.
DT Article
LA English
AB Objective: In the light of a reported 30-40% prevalence of pulmonary embolism (PE) in intermediate probability lung scans (IPLS) based on results of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, we examined the frequency of documented PE in 82 patients with IPLS, the management strategy employed in these patients with regards to additional imaging (e.g. further evaluation with venous sonography or spiral computed tomographic angiography (***CTA***)), anticoagulation therapy, and subsequent follow-up outcomes. Method: Retrospective ***review*** of the medical records of 82 patients with intermediate probability ventilation-perfusion (V/Q) lung scans from January 1998 to July 1999. Results: 14.1% of V/Q scans were reported as having an intermediate probability of PE. 72% of IPLS were subject to further evaluation with venous Doppler ultrasound and/or ***CTA*** , and 39% of these patients had evidence of thrombo-embolic disease. All patients with imaging evidence of thrombo-embolic disease were started on anticoagulation therapy. In addition, 19 patients were treated based on clinical judgement. Amongst the 35 patients who were not treated, 17 (49%) were based on clinical findings without further imaging. There was no mortality on follow-up of 28 cases of untreated IPLS. Conclusion: The majority of IPLS will have further imaging, out of which over one-third will have thrombo-embolic disease. Approximately half of IPLS cases will receive anticoagulation therapy. No mortality or PE was found on follow-up of patients who were not treated.

L9 ANSWER 9 OF 64 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5
AN 2001:317479 BIOSIS
DN PREV200100317479
TI Cancer and autoimmunity: Autoimmune and rheumatic features in patients with malignancies.
AU Abu-Shakra, M.; Buskila, D.; Ehrenfeld, M.; Conrad, K.; Shoenfeld, Y. (1)
CS (1) Department of Medicine B, Sheba Medical Centre, Tel-Hashomer, 52621: Shoenfel@post.tau.ac.il Israel
SO Annals of the Rheumatic Diseases, (May, 2001) Vol. 60, No. 5, pp. 433-440. print.
ISSN: 0003-4967.
DT General Review
LA English
SL English
AB Objectives-To ***review*** the autoimmune and rheumatic manifestations of patients with malignancy. Methods-A Medline search of all published papers using keywords related to malignancies, autoimmunity, rheumatic diseases, and paraneoplastic syndromes. Results-Patients with malignant diseases may develop autoimmune phenomena and rheumatic diseases as a result of (a) generation of autoantibodies against various autoantigens, including oncoproteins (P185, 1-myc, c-myc, c-myb), tumour suppression genes (P53), proliferation associated antigens (cyclin A, B1, D1, E; CENP-F; CDK, U3-RNP), onconeural antigens (Hu, Yo, Ri, Tr), ***cancer*** / ***testis*** ***antigens*** (MAGE, GAGE, BAGE, SSX, ESO, SCP, CT7), and rheumatic disease associated antigens (RNP, Sm). The clinical significance of the various autoantibodies is not clear. Anti-oncoprotein and anti-tumor suppression gene antigens are detected before the diagnosis of the cancer or in the early stages of the malignant disease, suggesting a potential diagnostic or prognostic role. Anti-onconeural antibodies are pathogenic and are associated with specific clinical neurological syndromes (anti-Hu syndrome and others). (b) Paraneoplastic syndromes, a wide range of clinical syndromes, including classic autoimmune rheumatic diseases that develop among patients with cancer. (c) Rheumatism after chemotherapy, a clinical entity characterised by the development of musculoskeletal symptoms after combination chemotherapy for malignancy. Conclusion-Autoimmune and rheumatic features are not rare among patients with malignancies. They are the result of various diverse mechanisms and occasionally they may be associated with serious clinical entities.

L9 ANSWER 10 OF 64 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2002012257 EMBASE
TI Composite tissue allotransplantation (***CTA***): Current status and future insights.
AU Gorantla V.; Maldonado C.; Frank J.; Barker J.H.
CS Dr. J.H. Barker, Plastic/Hand Surgery Research, 320, MDR Building, 511, South Floyd Street, Louisville, KY 40292, United States. jhbark01@athena.louisville.edu
SO European Journal of Trauma, (2001) 27/6 (267-274).
Refs: 58
ISSN: 1439-0590 CODEN: EJTRFM
CY Germany
DT Journal; General Review
FS 008 Neurology and Neurosurgery

009 Surgery
011 Otorhinolaryngology
027 Biophysics, Bioengineering and Medical Instrumentation
033 Orthopedic Surgery
LA English
SL English
AB Approximately 7 million individuals (over 1 million amputees) require complex reconstructive procedures in the United States each year. The recent success of clinical composite tissue allotransplantation, attests to the fact that composite tissue allografts have tremendous potential in these life-enhancing reconstructions. This ***review*** summarizes the initial outcomes of the first four human hand transplants, together with those of the first larynx, bone, knee, nerve and tendon transplants, with special emphasis on the operative technique, graft survival and functional outcomes. The May 2000 Louisville symposium, where these results were presented was undoubtedly a milestone in the history of modern composite tissue allotransplantation. It set the stage for reconstructive and transplant surgeons, researchers, physiotherapists, patients and patient advocates and members of the community to convene and discuss major advances in current composite tissue allotransplantation. The symposium underscored the vital importance of objective evaluation of the status of composite tissue allotransplantation by frank dissemination of details of clinical results and complications of the transplants performed thus far. The composite tissue allotransplantation area is among the newest of transplant areas. The immunology of composite tissue allografts is complex, making tolerance more difficult to achieve than organ tolerance. It needs to be emphasized that any episodes of acute rejection should be prevented for perfect restoration of function and to minimize the risk of chronic rejection in composite tissue allografts. Efficacious, safe and ethical clinical tolerance protocols could improve patient acceptance of composite tissue allografts by providing an alternative to chronic immunosuppression.

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(FILE 'HOME' ENTERED AT 14:18:30 ON 11 APR 2002)

FILE 'BIOSIS, MEDLINE, EMBASE' ENTERED AT 14:18:37 ON 11 APR 2002
E DE SANTIS/AU
L1 224 S DE SANTIS R/AU
L2 13 S DE SANTIS RITA/AU
L3 43464 S ANTIGEN PRESENTING CELL? OR APC
L4 27249 S HYPOMETHYLAT? OR DEMETHYLAT? OR UNMETHYLAT?
L5 52 S L3 (S) L4
L6 24 DUP REM L5 (28 DUPLICATES REMOVED)
L7 3494 S CANCER TESTIS ANTIGEN? OR CTA
L8 94 S L7 AND REVIEW
L9 64 DUP REM L8 (30 DUPLICATES REMOVED)

=> s cancer testis antigen?
L10 152 CANCER TESTIS ANTIGEN?

=> s l10 and review
L11 7 L10 AND REVIEW

=> dup rem l11
PROCESSING COMPLETED FOR L11
L12 5 DUP REM L11 (2 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 5 ANSWERS - CONTINUE? Y/(N):y

L12 ANSWER 1 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2002093017 EMBASE
TI ***Cancer*** / ***testis*** ***antigens*** : Structural and immunobiological properties.
AU Kirkin A.F.; Dzhandzhugazyan K.N.; Zeuthen J.
CS Dr. J. Zeuthen, Department of Tumor Cell Biology, Institute of Cancer Biology, Danish Cancer Society, Strandboulevarden 49, DK-2100 Copenhagen, Denmark. jz@cancer.dk
SO Cancer Investigation, (2002) 20/2 (222-236).
Refs: 106
ISSN: 0735-7907 CODEN: CINVD7
CY United States
DT Journal; General Review
FS 016 Cancer
026 Immunology, Serology and Transplantation
028 Urology and Nephrology
LA English
SL English
AB Characterization of tumor-associated antigens recognized by cytotoxic T lymphocytes which has evolved during recent years opens new possibilities for specific anti-cancer immunotherapy. Among different groups of tumor-associated antigens, cancer/testis (CT) antigens (expressed in many tumors and among normal tissues only in testes) represent the most perspective antigens for immunotherapy because of their broad tumor-specific expression. More than 50 CT antigens have been described so far and, for many of them, epitopes recognized by T lymphocytes have been identified. The most studied group of CT antigens is the MAGE proteins, which form the so-called MAGE superfamily, together with some MAGE-like proteins that have a different distribution than classical CT antigens. The MAGE superfamily includes five families: MAGE-A, MAGE-B, MAGE-C, MAGE-D, and necdin. Comparison of the structure of members of MAGE superfamily points to the existence of a domain organization of these proteins. The central, core domain (second domain) is highly conservative. The first domain is homologous among MAGE family members with a CT expression, but unique for each member of the MAGE-D and necdin families. In addition to the homology of the central domain, the third domain is also homologous among all members of MAGE superfamily, but to a much lesser extent. The MAGE-D proteins contain an additional, fourth domain, which in the case of MAGE-D3 coincides with trophinin, a separate molecule described previously as an adhesion molecule that participates in embryo implantation. The structural classification of the members of MAGE superfamily might help in the future to understand the biological function of MAGE proteins. One important property of the CT antigens is the up-regulation of their expression by DNA demethylating agents, indicating a possible mechanism for their reexpression in tumors. One of the implications of this particular property could be that a combination of immunotherapy targeting CT antigens with chemotherapy inducing up-regulation of CT antigens might result in more efficient tumor eradication.

L12 ANSWER 2 OF 5 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
AN 2001:317479 BIOSIS
DN PREV200100317479
TI Cancer and autoimmunity: Autoimmune and rheumatic features in patients with malignancies.
AU Abu-Shakra, M.; Buskila, D.; Ehrenfeld, M.; Conrad, K.; Shoenfeld, Y. (1)
CS (1) Department of Medicine B, Sheba Medical Centre, Tel-Hashomer, 52621: Shoenfel@post.tau.ac.il Israel
SO Annals of the Rheumatic Diseases, (May, 2001) Vol. 60, No. 5, pp. 433-440. print.
ISSN: 0003-4967.
DT General Review
LA English
SL English
AB Objectives-To ***review*** the autoimmune and rheumatic manifestations of patients with malignancy. Methods-A Medline search of all published papers using keywords related to malignancies, autoimmunity, rheumatic diseases, and paraneoplastic syndromes. Results-Patients with malignant diseases may develop autoimmune phenomena and rheumatic diseases as a result of (a) generation of autoantibodies against various autoantigens, including oncoproteins (P185, 1-myc, c-myc, c-myb), tumour suppression genes (P53), proliferation associated antigens (cyclin A, B1, D1, E; CENP-F; CDK, U3-RNP), onconeural antigens (Hu, Yo, Ri, Tr), ***cancer*** / ***testis*** ***antigens*** (MAGE, GAGE, BAGE, SSX, ESO, SCP, CT7), and rheumatic disease associated antigens (RNP, Sm). The clinical significance of the various autoantibodies is not clear. Anti-oncoprotein and anti-tumor suppression gene antigens are detected before the diagnosis of the cancer or in the early stages of the malignant disease, suggesting a potential diagnostic or prognostic role. Anti-onconeural antibodies are pathogenic and are associated with specific clinical neurological syndromes (anti-Hu syndrome and others). (b) Paraneoplastic syndromes, a wide range of clinical syndromes, including classic autoimmune rheumatic diseases that develop among patients with cancer. (c) Rheumatism after chemotherapy, a clinical entity characterised by the development of musculoskeletal symptoms after combination chemotherapy for malignancy. Conclusion-Autoimmune and rheumatic features are not rare among patients with malignancies. They are the result of various diverse mechanisms and occasionally they may be associated with serious clinical entities.

L12 ANSWER 3 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2000147204 EMBASE
TI Cancer genetics/epigenetics and the X chromosome: Possible new links for malignant glioma pathogenesis and immune-based therapies.
AU Mintz A.; Debinski W.
CS Dr. W. Debinski, Section of Neurosurgery, Department of Surgery, Pennsylvania State Univ. Coll. Med., 500 University Drive, Hershey, PA 17033-0850, United States. wdebinski@psghs.edu
SO Critical Reviews in Oncogenesis, (2000) 11/1 (77-95).
Refs: 136
ISSN: 0893-9675 CODEN: CRONEI
CY United States
DT Journal; General Review
FS 008 Neurology and Neurosurgery
016 Cancer
022 Human Genetics
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Human high-grade gliomas (HGGs) are rapidly progressing heterogeneous brain tumors of unknown etiology and there are no effective treatment modalities available. The recent discovery of cancer-specific antigens has opened new doors for specific tumor-targeted treatments using passive and active immunotherapeutic strategies. In particular, SEREX (serological analysis of recombinant CDNA expression libraries) has aided in the discovery of numerous new tumor antigens. These specific tumor antigens are located on chromosome X and are expressed predominantly in the testes among normal organs, and hence termed ***Cancer*** / ***Testis*** ***Antigens*** (CTAs). We found that the vast majority of HGG patients overexpress a receptor for an immune regulatory cytokine, interleukin 13 (IL-13), which differs from the normal tissue physiological receptor.

Interestingly, the HGG-associated receptor protein, IL-13R.alpha., is expressed solely in the testes and its gene is localized to chromosome X, which mirror the expression pattern and genomic localization of CTAs. There is little evidence for frequent gross structural abnormalities on chromosome X in HGG. Although the mechanism that causes X chromosome-linked CTAs to be aberrantly expressed in tumors is not fully understood, evidence is beginning to point toward the DNA methylation dysregulation that occurs in tumor cells as being implicit in this process and perhaps in the oncogenic process as well. Therefore, further study of the phenomenon of CTAs may bring the dual benefit of better understanding tumorigenesis and providing new molecular tools for better management of HGGs. Also, we propose that the X chromosome may in fact be an important player in HGG oncogenesis.

L12 ANSWER 4 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2000370789 EMBASE
TI Challenges in the specific immunotherapy of cancer.
AU Jager E.; Jager D.; Knuth A.
CS E. Jager, II. Medizinische Klinik, Hamatologie-Onkologie, Krankenhaus Nordwest, Steinbacher Hohl 2-26, 60488 Frankfurt am Main, Germany
SO Gann Monographs on Cancer Research, (1999) 48/- (191-199).
Refs: 47
ISSN: 0072-0151 CODEN: GANMAX
CY Japan
DT Journal; General Review
FS 013 Dermatology and Venereology
016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB The characterization of tumor-associated antigens recognized by cellular or humoral effectors of the immune system has opened new perspectives for cancer therapy. Several categories of cancer-associated antigens have been described as targets for cytotoxic T lymphocytes (CTL) in vitro and in vivo: 'Cancer Testis' (CT) antigens expressed in different tumors and normal testis, melanocyte differentiation antigens, point mutations of normal genes, antigens that are overexpressed in malignant tissues, and viral antigens. Clinical studies with peptides derived from these antigens have been initiated to induce specific CTL responses in vivo. Immunological and clinical parameters for the assessment of peptide-specific reactions have been defined, i.e. induction of delayed-type hypersensitivity (DTH-), CTL-, autoimmmune-, and tumor regression responses. Preliminary results demonstrate that tumor-associated peptides alone elicit specific DTH- and CTL responses leading to tumor regression after intradermal injection. Granulocyte macrophage colony-stimulating factor was proven effective to enhance peptide-specific immune reactions by amplification of dermal peptide-presenting dendritic cells. Long-lasting complete tumor regressions have been observed after induction of CTL by peptide immunization. However, in single cases with disease progression after an initial tumor response either a loss of the respective tumor antigen targeted by CTL or of the presenting major histocompatibility complex (MHC) class I molecule was detected as mechanisms of immune escape under immunization in vivo. Based on these observations, cytokines to enhance antigen- and MHC class I expression in vivo are being evaluated to prevent immunoselection. Recently, a strategy utilizing spontaneous antibody responses to tumor-associated antigens (SEREX) has led to the identification of a new cancer-testis (CT) antigen, NY-ESO-1. In a melanoma patient with high titer antibody against NY-ESO-1 a strong human leukocyte antigen (HLA)-A2 restricted CTL reactivity against the same antigen was also found. Clinical studies involving tumor antigens that induce both antibody- and CTL responses will show whether these are better candidates for immunotherapy of cancer. Passive immunotherapeutic approaches with monoclonal antibodies or adoptive transfer of CTL clones targeting tumor-associated antigens, as well as active immunization with ganglioside antigens to induce specific antibody responses in vivo are being evaluated. Complementary use of specific active and passive immunization may improve clinical effects and prevent immune escape in vivo.

L12 ANSWER 5 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998357824 EMBASE
TI Development of new immunotherapies using melanoma antigens recognized by T
cells.
AU Kawakami Y.
CS Dr. Y. Kawakami, Division of Cellular Signaling, Institute for Advanced Medicine, University School of Medicine, 35 Shinano-machi, Shinjuku-ku, Tokyo 160-8582, Japan
SO Biotherapy, (1998) 12/9 (1187-1194).
Refs: 28
ISSN: 0914-2223 CODEN: BITPE
CY Japan
DT Journal; General Review
FS 016 Cancer
026 Immunology, Serology and Transplantation
LA Japanese
SL English; Japanese
AB Melanoma is a relatively immunogenic cancer and a good model to evaluate the possibilities of immunotherapies. Recent progress of molecular biology and immunology has allowed us to understand immune responses to human cancer at the molecular level. Although antigens for CD4+ T cells have not well been identified, various melanoma antigens recognized by CD8+ T cells have been identified, including tissue specific proteins (melanosomal proteins), proteins expressed in testis and a variety of cancers (***Cancer*** - ***Testis*** ***antigens***) and tumor specific mutated proteins. The immunological features of these antigens have been characterized for development of new immunotherapies. Based on these findings, antigen specific immunotherapies have been developed. Some of the phase I clinical trials with the identified melanoma antigens demonstrated anti-tumor effects. Immunization with the modified gp100 epitope that had high MHC binding affinity, in conjunction with incomplete freund adjuvant and high-dose IL-2, resulted in a 42 % response rate (CR+PR). Immunization with dendritic cells pulsed with tumor lysates or epitope peptides resulted in a 31 % response rate in metastatic melanoma. These immunotherapies need to be improved through modifications and better understanding of tumor escape mechanisms.

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(FILE 'HOME' ENTERED AT 14:18:30 ON 11 APR 2002)

FILE 'BIOSIS, MEDLINE, EMBASE' ENTERED AT 14:18:37 ON 11 APR 2002
E DE SANTIS/AU
L1 224 S DE SANTIS R/AU
L2 13 S DE SANTIS RITA/AU
L3 43464 S ANTIGEN PRESENTING CELL? OR APC
L4 27249 S HYPOMETHYLAT? OR DEMETHYLAT? OR UNMETHYLAT?
L5 52 S L3 (S) L4
L6 24 DUP REM L5 (28 DUPLICATES REMOVED)
L7 3494 S CANCER TESTIS ANTIGEN? OR CTA
L8 94 S L7 AND REVIEW
L9 64 DUP REM L8 (30 DUPLICATES REMOVED)
L10 152 S CANCER TESTIS ANTIGEN?
L11 7 S L10 AND REVIEW
L12 5 DUP REM L11 (2 DUPLICATES REMOVED)

=> s cancer associated antigen? or tumor associated antigen?
L13 10042 CANCER ASSOCIATED ANTIGEN? OR TUMOR ASSOCIATED ANTIGEN?

=> s l7 and l4
L14 24 L7 AND L4

=> dup rem l14
PROCESSING COMPLETED FOR L14
L15 11 DUP REM L14 (13 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 11 ANSWERS - CONTINUE? Y/(N):y

L15 ANSWER 1 OF 11 MEDLINE
AN 2002189894 IN-PROCESS
DN 21920357 PubMed ID: 11922625
TI Identification and Characterization of a Novel ***Cancer*** / ***Testis*** ***Antigen*** Gene CAGE.
AU Cho Bomsoo; Lim Yoon; Lee Dae-Yeon; Park Sae-Young; Lee Hosoon; Kim Woo
Ho; Yang Hankwang; Bang Yung-Jue; Jeoung Doo-Il
CS Cancer Genomics Division, In2Gen Company, Seoul, 110-799, Korea.
SO BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2002 Apr 5) 292 (3)
715-26.
Journal code: 0372516. ISSN: 0006-291X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20020403
Last Updated on STN: 20020403
AB We applied serological analysis of cDNA expression library technique to identify cancer-associated genes. We screened cDNA expression libraries of human testis and gastric cancer cell lines with sera of patients with gastric cancers. We identified a gene whose expression is testis-specific among normal tissues. We cloned and characterized this novel gene. It contains D-E-A-D box domain and encodes a putative protein of 630 amino acids with possible helicase activity. It showed wide expression in various cancer tissues and cancer cell lines. The corresponding gene was named cancer-associated gene (CAGE). PCR of human x hamster Radiation Hybrids showed localization of CAGE on the human chromosome Xp22. Transient transfection of CAGE showed predominantly nuclear localization. Both Western blot and plaque assay indicated seroreactivity of CAGE protein. We found that ***demethylation*** played a role in the activation of CAGE in some cancer cell lines that do not express it. Cell synchronization experiments showed that the expression of CAGE was related with cell cycle. This suggests that CAGE might play a role in cellular proliferation. Because CAGE is expressed in a variety of cancers but not in normal tissues except testis, this gene can be a target of antitumor immunotherapy. (c)2002 Elsevier Science (USA).

L15 ANSWER 2 OF 11 MEDLINE DUPLICATE 1
AN 2002170533 IN-PROCESS
DN 21899576 PubMed ID: 11901543

TI ***Cancer*** / ***testis*** ***antigens*** : structural and immunobiological properties.
AU Kirkin Alexei F; Dzhandzhugazyan Karine N; Zeuthen Jesper
CS Department of Tumor Cell Biology, Institute of Cancer Biology, Danish.
SO CANCER INVESTIGATION, (2002) 20 (2) 222-36.
Journal code: 8307154. ISSN: 0735-7907.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20020321
Last Updated on STN: 20020321
AB Characterization of tumor-associated antigens recognized by cytotoxic T lymphocytes which has evolved during recent years opens new possibilities for specific anti-cancer immunotherapy. Among different groups of tumor-associated antigens, cancer/testis (CT) antigens (expressed in many tumors and among normal tissues only in testes) represent the most perspective antigens for immunotherapy because of their broad tumor-specific expression. More than 50 CT antigens have been described so far and, for many of them, epitopes recognized by T lymphocytes have been identified. The most studied group of CT antigens is the MAGE proteins, which form the so-called MAGE superfamily, together with some MAGE-like proteins that have a different distribution than classical CT antigens. The MAGE superfamily includes five families: MAGE-A, MAGE-B, MAGE-C, MAGE-D, and necdin. Comparison of the structure of members of MAGE superfamily points to the existence of a domain organization of these proteins. The central, core domain (second domain) is highly conservative. The first domain is homologous among MAGE family members with a CT expression, but unique for each member of the MAGE-D and necdin families. In addition to the homology of the central domain, the third domain is also homologous among all members of MAGE superfamily, but to a much lesser extent. The MAGE-D proteins contain an additional, fourth domain, which in the case of MAGE-D3 coincides with trophinin, a separate molecule described previously as an adhesion molecule that participates in embryo implantation. The structural classification of the members of MAGE superfamily might help in the future to understand the biological function of MAGE proteins. One important property of the CT antigens is the up-regulation of their expression by DNA ***demethylating*** agents, indicating a possible mechanism for their re-expression in tumors. One of the implications of this particular property could be that a combination of immunotherapy targeting CT antigens with chemotherapy inducing up-regulation of CT antigens might result in more efficient tumor eradication.

L15 ANSWER 3 OF 11 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2
AN 2002:120300 BIOSIS
DN PREV200200120300
TI Promoter methylation controls the expression of MAGE2, 3 and 4 genes in human cutaneous melanoma.
AU Sigalotti, Luca; Coral, Sandra; Nardi, Gianpaolo; Spessotto, Alberto; Cortini, Enzo; Cattarossi, Ilaria; Colizzi, Francesca; Altomonte, Maresa; Maio, Michele (1)
CS (1) Cancer Bioimmunotherapy Unit, Centro di Riferimento Oncologico, I.R.C.C.S., Via Pedemontana Occ.le 12, 33081, Aviano: mmaio@cro.it Italy
SO Journal of Immunotherapy, (January February, 2002) Vol. 25, No. 1, pp. 16-26. print.
ISSN: 1524-9557.
DT Article
LA English
AB ***Cancer*** - ***testis*** ***antigens*** expressed by different-histotype transformed cells are suitable targets for tumor immunotherapy. However, their heterogeneous expression in neoplastic lesions limits the eligibility of patients for ***cancer*** - ***testis*** ***antigen*** -directed vaccination, and low levels of ***cancer*** - ***testis*** ***antigens*** ' expression may impair immune recognition of malignant cells. Because of the primary clinical relevance of ***cancer*** - ***testis*** ***antigens*** ' expression in neoplastic tissues, 68 unrelated or sequential metastatic lesions from 56 patients were used to characterize the molecular mechanisms regulating the presence and levels of expression of different ***cancer*** - ***testis*** ***antigens*** of the MAGE family (i.e., MAGE2, 3 and 4) in cutaneous melanoma. Polymerase chain reaction-based methylation analyses showed that methylation status of specific cytosine-guanine dinucleotides in the promoters of investigated ***cancer*** - ***testis*** ***antigens*** correlated with their heterogeneous expression within unrelated metastatic melanoma lesions, and with their homogeneous expression among sequential metastases from three patients with melanoma. Unlike methylated promoters, ***unmethylated*** promoters of MAGE2, 3 and 4 genes drove the expression of reporter gene-enhanced green fluorescent protein after transient transfection of ***cancer*** - ***testis*** ***antigen*** -positive Mel 142 melanoma cells. Furthermore, de novo expression of MAGE3 gene induced by the treatment of Mel 195 melanoma cells with the DNA ***hypomethylating*** agent 5-aza-2'-deoxycytidine was associated with a 6%-12% ***demethylation*** of selected cytosine-guanine dinucleotides in its promoter. Finally, 5-aza-2'-deoxycytidine induced a 16-fold increase of MAGE3 expression in Mel 313 melanoma cells expressing constitutively low levels of the antigen, but did not affect that of Mel 275 melanoma cells expressing high baseline levels of MAGE3. Overall, these findings identify promoter methylation as a shared mechanism directly regulating the expression of therapeutic ***cancer*** - ***testis*** ***antigens*** in metastatic melanomas, and foresee the clinical use of 5-aza-2'-deoxycytidine to design new chemoimmunotherapeutic strategies in patients with melanoma.

L15 ANSWER 4 OF 11 MEDLINE DUPLICATE 3
AN 2001149815 MEDLINE
DN 21084599 PubMed ID: 11216765
TI Induction of MAGE-3 expression in lung and esophageal cancer cells.
AU Weiser T S; Ohnmacht G A; Guo Z S; Fischette M R; Chen G A; Hong J A; Nguyen D M; Schrump D S
CS Thoracic Oncology Section, Surgery Branch, National Cancer Institute, Bethesda, Maryland 20892-1502, USA.
SO ANNALS OF THORACIC SURGERY, (2001 Jan) 71 (1) 295-301; discussion 301-2.
Journal code: 683; 15030100R. ISSN: 0003-4975.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200103
ED Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315
AB BACKGROUND: Although MAGE-3 has been detected in approximately 40% of lung and esophageal cancers, expression of this ***cancer*** ***testis*** ***antigen*** appears to be below the threshold for immune recognition in patients with these malignancies. The aim of this study was to determine if the ***demethylating*** agent, 5-Aza-2'-deoxycytidine (DAC) and if the histone deacetylase inhibitor Depsipeptide FR901228 (DP) could enhance MAGE-3 expression in lung and esophageal cancer cells. METHODS: Eleven lung and esophageal cancer lines and cultured normal human bronchial epithelial (NHBE) cells were exposed to normal media (NM), DAC, DP, or combination DAC/DP at varying concentrations and exposure durations. MAGE-3 expression was evaluated by quantitative RT-PCR (TaqMan) and immunohistochemistry techniques. Trypan blue exclusion techniques were used to examine the proliferation of cancer cells after drug exposure. RESULTS: Relative to untreated controls, MAGE-3 expression was enhanced 32-fold (range 3.9 to 110) by DAC alone (0.1 micromol/L x 72 h), 2.1-fold (0.4 to 4.2) by DP alone (25 ng/mL x 6h), and 57-fold (4.6 to 209) by sequential DAC/DP exposure. Increased MAGE-3 mRNA copy numbers coincided with enhanced protein levels in these cells. MAGE-3 expression persisted after drug exposure. Flow cytometry confirmed the presence of functional HLA class I expression in these cells. Sequential DAC/DP treatment mediated pronounced growth inhibition in cancer cells but not NHBE. CONCLUSIONS: Sequential DAC/DP treatment may be a novel strategy to simultaneously augment MAGE-3 expression and induce growth arrest in thoracic malignancies.

L15 ANSWER 5 OF 11 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
4
AN 2001:332923 BIOSIS
DN PREV200100332923
TI Sequential 5-Aza-2'-deoxycytidine-depsipeptide FR901228 treatment induces apoptosis preferentially in cancer cells and facilitates their recognition by cytolytic T lymphocytes specific for NY-ESO-1.
AU Weiser, Todd S.; Guo, Z. Sheng; Ohnmacht, Galen A.; Parkhurst, Maria L.; Tong-On, Panida; Marincola, Francesco M.; Fischette, Maria R.; Yu, Xiaodan; Chen, G. Aaron; Hong, Julie A.; Stewart, John H.; Nguyen, Dao M.; Rosenberg, Steven A.; Schrump, David S. (1)
CS (1) Surgery Branch, National Cancer Institute, 10 Center Drive, Building 10, Room 2B-07, Bethesda, MD, 20892-1502: David_Schrump@nih.gov USA
SO Journal of Immunotherapy, (March April, 2001) Vol. 24, No. 2, pp. 151-161. print.
ISSN: 1524-9557.
DT Article
LA English
SL English
AB Global alterations in chromatin structure profoundly influence gene expression in thoracic neoplasms, silencing tumor suppressors while facilitating the expression of various ***cancer*** ***testis*** ***antigens*** such as NY-ESO-1. Although recent studies have shown that histone deacetylase inhibitors can potentiate tumor suppressor gene induction mediated by ***demethylating*** agents in cancer cells, the ability of these agents to augment ***cancer*** ***testis*** ***antigen*** expression have not been fully defined. The authors designed the current study to determine whether the histone deacetylase inhibitor, depsipeptide FR901228 (DP), could enhance NY-ESO-1 induction mediated by the DNA ***demethylating*** agent 5-Aza-2'-deoxycytidine (DAC) in cell lines established primarily from thoracic cancers. Quantitative reverse-transcriptase polymerase chain reaction analysis revealed that, under exposure conditions potentially achievable in clinical settings, DAC dramatically induced NY-ESO-1 expression in cultured cancer lines. DP alone mediated negligible target gene induction but significantly augmented DAC-mediated induction of NY-ESO-1. After DAC or sequential DAC-DP treatment, HLA-A*0201 cancer cells were recognized by an HLA-A*0201 CTL specific for NY-ESO-1. Although sequential DAC/DP exposure did not uniformly enhance immune recognition of target cells compared with DAC alone, this treatment mediated profound induction of

apoptosis in cancer cells but not normal human bronchial epithelia. The apoptotic effects of DAC, DP, or sequential DAC-DP did not correlate in an obvious manner with histology, or the magnitude of NY-ESO-1 induction in cancer cells. Although the mechanisms have not been fully defined, sequential DAC-DP treatment may be a novel strategy to augment antitumor immunity in cancer patients.

L15 ANSWER 6 OF 11 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5
AN 2000:188621 BIOSIS
DN PREV200000188621
TI Heterogeneous expression of the SSX ***cancer*** / ***testis*** ***antigens*** in human melanoma lesions and cell lines.
AU dos Santos, Nuno R. (1); Torensma, Ruurd; de Vries, Teunis J.; Schreurs, Marco W. J.; de Bruijn, Diederik R. H.; Kater-Baats, Ellen; Ruiter, Dirk J.; Adema, Gosse J.; van Muijen, Goos N. P.; van Kessel, Ad Geurts
CS (1) University Hospital Nijmegen, 6500 HB, Nijmegen Netherlands
SO Cancer Research, (March 15, 2000) Vol. 60, No. 6, pp. 1654-1662. ISSN: 0008-5472.
DT Article
LA English
SL English
AB The SSX genes, located on the X chromosome, encode a family of highly homologous nuclear proteins. The SSX1 and SSX2 genes were initially identified as fusion partners of the SYT gene in t(X;18)-positive synovial sarcomas. Recently, however, it was found that these two genes, as well as the highly homologous SSX4 and SSX5 genes, are aberrantly expressed in different types of cancers, including melanomas. Because normal SSX expression has been detected only in the testis and, at very low levels, the thyroid, these proteins are considered as new members of the still growing family of ***cancer*** / ***testis*** ***antigens*** . These antigens are presently considered as targets for the development of cancer immunotherapy protocols. In the present study, we developed a monoclonal antibody found to recognize SSX2, SSX3, and SSX4 proteins expressed in formaldehyde-fixed and paraffin-embedded tissues. This antibody was used to investigate SSX expression in normal testis and thyroid, benign melanocytic lesions, melanoma lesions, and melanoma cell lines. SSX nuclear expression in the testis was found to be restricted to spermatogenic cells, mainly spermatogonia. Of 18 melanoma cell lines analyzed, 9 showed SSX RNA and protein expression, although heterogeneously and at variable levels. Treatment of an SSX-negative cell line with 5-aza-2'-deoxycytidine, a ***demethylating*** agent, led to SSX RNA and protein expression, indicating a role for methylation in transcription regulation. Thirty-four of 101 primary and metastatic melanoma cases and 2 of 24 common nevocellular and atypical nevus cases showed SSX nuclear staining. Again, SSX expression was heterogeneous, ranging from widespread to scarce. Our findings stress the importance of assessing the a priori SSX expression status of melanoma cases that may be selected for immunotherapeutic trials.

L15 ANSWER 7 OF 11 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2000:458577 BIOSIS
DN PREV200000458577
TI Promoter methylation directly controls the expression of MAGE-2, -3 and -4 genes in cutaneous melanoma.
AU Sigalotti, L. (1); Coral, S. (1); Nardi, G. (1); Spessotto, A. (1); Cattarossi, I. (1); Colizzi, F. (1); Altomonte, M. (1); Maio, M. (1)
CS (1) Advanced Immunotherapy Unit, Centro di Riferimento Oncologico, I.N.R.C.C.S., 33081, Aviano Italy
SO Journal of Immunotherapy, (September October, 2000) Vol. 23, No. 5, pp. 607. print.
Meeting Info.: 15th Annual Scientific Meeting of the Society for Biological Therapy Seattle, Washington, USA October 26-29, 2000 Society for Biological Therapy
.
DT Conference
LA English
SL English

L15 ANSWER 8 OF 11 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2000:224655 BIOSIS
DN PREV200000224655
TI Cancer genetics/epigenetics and the X chromosome: Possible new links for malignant glioma pathogenesis and immune-based therapies.
AU Mintz, Akiva; Debinski, Waldemar (1)
CS (1) Section of Neurosurgery/H110, Department of Surgery, Pennsylvania State University College of Medicine, 500 University Drive, Hershey, PA, 17033-0850 USA
SO Critical Reviews in Oncogenesis, (2000) Vol. 11, No. 1, pp. 77-95. ISSN: 0893-9675.
DT General Review
LA English
SL English

L15 ANSWER 9 OF 11 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
6
AN 1993:211184 BIOSIS
DN PREV199395112409
TI In vivo and in vitro stereoselective metabolism of mianserin in mice.
AU Heinig, R. (1); Blaschke, G.
CS (1) Inst. Pharmazeutische Chemie, Univ. Muenster, Hittorfstr. 58-62, W-4400 Muenster/Westf. Germany
SO Arzneimittel-Forschung, (1993) Vol. 43, No. 1, pp. 5-10. ISSN: 0004-4172.
DT Article
LA English
SL English; German
AB The preparative separation of mianserin (CAS 2419-97-4) enantiomers, both of unlabelled compound in g-amounts and radiolabelled compound as used for metabolism studies in mu-g-amounts, is facilitated by means of LC on microcyrstalline cellulose triacetate (***CTA***). HPLC on ***CTA*** is used for confirmation of the enantiomeric purity. After administration of 14C-labelled enantiomers to mice AUC and C-max of the S-enantiomer were increased by 48% and 128%, resp. With regard to urinary metabolites from rac mianserin 97.9% of the radioactivity was excreted in conjugated form. Glucuronidation (82.1%) was preferred to sulphation (15.8%). The excretion of N- ***demethylated*** metabolites was increased after dosage or R-mianserin, demonstrated by an R:S ratio of 5.2 (8-hydroxy-demethylmianserin glucuronide), while the S-enantiomer was mainly metabolized to 8-hydroxymianserin glucuronide (S:R+3.2). The 8-hydroxymianserin N(2) oxide was selective for the S-isomer. In mouse liver homogenate with NADPH as cosubstrate the overall extent of metabolism was greater for R-mianserin (87.1% R vs. 444.1%S). The R-enantiomer prefers N- ***demethylation*** (R:S=3.4-4.0) while more N-oxidized metabolites are formed from S-mianserin (S:R=2.5), which is in agreement with published data on human liver microsomes (5). The reported stereoselectivities were confirmed in liver homogenates of both male and female mice, whereas the extent of N- ***demethylation*** and N-oxidation was dependent on the gender. The in vitro data suggest that hepatic metabolism of mianserin is stereoselective. N- ***demethylation*** and N-oxidation demonstrate opposite stereoselectivities, which is also reflected in the urinary metabolic pattern of the enantiomers. The preferred Cytochrome P-450-mediated conversion of the R-enantiomer is likely to be responsible for the observed differences in the plasma levels of R- and S-mianserin.

L15 ANSWER 10 OF 11 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
7
AN 1982:167247 BIOSIS
DN BA73:27231
TI CHEMICAL AND BIOCHEMICAL CHARACTERISTICS OF O ***DEMETHYLATION*** OF CHLOROTRIANISENE IN THE RAT.
AU RUENITZ P C; TOLEDO M M
CS SCH. OF PHARMACY, UNIV. OF GEORGIA, ATHENS, GA 30602, USA.
SO BIOCHEM PHARMACOL, (1981) 30 (16), 2203-2208. CODEN: BCPCA6. ISSN: 0006-2952.
FS BA; OLD
LA English
AB The effects of NADPH concentration and of 2 inhibitors of the microsomal mixed function oxidase system [2-diethylaminoethyl-2,2-diphenyl valerate hydrochloride (SKF 525-A) and metyrapone] on rat liver microsomal O- ***demethylation*** of the triphenylethylene estrogen chlorotrianisene (***CTA***) were studied. Comparative data were obtained using untreated and phenobarbital-pretreated rats of both sexes. In the presence of microsomes from males, O- ***demethylation*** was induced slightly by phenobarbital (PB), and it was inhibited substantially by SKF 525-A, particularly with uninduced microsomes. Metyrapone had little inhibitory effect. In the presence of microsomes from females, O- ***demethylation*** was not induced by PB and inhibited significantly by SKF 525-A or metyrapone. Incubation of ***CTA*** with male rat microsomes afforded, after purification, a mixture of monophenolic metabolites which consisted primarily of a 1:1 mixture of E- and Z-desmethylchlorotrianisene.

L15 ANSWER 11 OF 11 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
8
AN 1979:182715 BIOSIS
DN BA67:62715
TI RABBIT HEPATIC MICROSOMAL O ***DEMETHYLATION*** OF CHLOROTRIANISENE.
AU RUENITZ P C
CS SCH. PHARM., UNIV. GA., ATHENS, GA. 30602, USA.
SO DRUG METAB DISPOS, (1978 (RECD 1979)) 6 (6), 631-636. CODEN: DMDSAI. ISSN: 0090-9556.
FS BA; OLD
LA English
AB The in vitro hepatic O- ***demethylation*** of the nonsteroidal estrogen chlorotrianisene (***CTA***) was studied. The rate of O- ***demethylation*** was maximal at 0.4 mM NADPH. Although NADH did not catalyze the reaction alone, it had a synergistic effect in the presence of equimolar amounts of NADPH. Carbon monoxide decreased the rate of O- ***demethylation*** . Nicotinamide was found to decrease the O- ***demethylation*** rate at a concentration of 40 mM, but had no apparent effect at concentrations of 20 mM or lower. Extracts from incubation mixtures contained one major (mono-O- ***demethylated***) and a minor (bis-O- ***demethylated***) metabolite. Extracts of mixtures containing soluble rather than microsomal enzymes or from mixtures in which microsomal protein was denatured did not contain these metabolites.

=> d his

(FILE 'HOME' ENTERED AT 14:18:30 ON 11 APR 2002)

FILE 'BIOSIS, MEDLINE, EMBASE' ENTERED AT 14:18:37 ON 11 APR 2002
E DE SANTIS/AU
L1 224 S DE SANTIS R/AU
L2 13 S DE SANTIS RITA/AU
L3 43464 S ANTIGEN PRESENTING CELL? OR APC
L4 27249 S HYPOMETHYLAT? OR DEMETHYLAT? OR UNMETHYLAT?
L5 52 S L3 (S) L4
L6 24 DUP REM L5 (28 DUPLICATES REMOVED)
L7 3494 S CANCER TESTIS ANTIGEN? OR CTA
L8 94 S L7 AND REVIEW
L9 64 DUP REM L8 (30 DUPLICATES REMOVED)
L10 152 S CANCER TESTIS ANTIGEN?
L11 7 S L10 AND REVIEW
L12 5 DUP REM L11 (2 DUPLICATES REMOVED)
L13 10042 S CANCER ASSOCIATED ANTIGEN? OR TUMOR ASSOCIATED ANTIGEN?
L14 24 S L7 AND L4
L15 11 DUP REM L14 (13 DUPLICATES REMOVED)

=> s l13 and l4
L16 4 L13 AND L4

=> dup rem l16
PROCESSING COMPLETED FOR L16
L17 2 DUP REM L16 (2 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 2 ANSWERS - CONTINUE? Y/(N):y

L17 ANSWER 1 OF 2 MEDLINE DUPLICATE 1
AN 2002170533 IN-PROCESS
DN 21899576 PubMed ID: 11901543
TI Cancer/testis antigens: structural and immunobiological properties.
AU Kirkin Alexei F; Dzhandzhugazyan Karine N; Zeuthen Jesper
CS Department of Tumor Cell Biology, Institute of Cancer Biology, Danish.
SO CANCER INVESTIGATION, (2002) 20 (2) 222-36.
Journal code: 8307154. ISSN: 0735-7907.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20020321
Last Updated on STN: 20020321
AB Characterization of ***tumor*** - ***associated*** ***antigens*** recognized by cytotoxic T lymphocytes which has evolved during recent years opens new possibilities for specific anti-cancer immunotherapy. Among different groups of ***tumor*** - ***associated*** ***antigens*** , cancer/testis (CT) antigens (expressed in many tumors and among normal tissues only in testes) represent the most perspective antigens for immunotherapy because of their broad tumor-specific expression. More than 50 CT antigens have been described so far and, for many of them, epitopes recognized by T lymphocytes have been identified. The most studied group of CT antigens is the MAGE proteins, which form the so-called MAGE superfamily, together with some MAGE-like proteins that have a different distribution than classical CT antigens. The MAGE superfamily includes five families: MAGE-A, MAGE-B, MAGE-C, MAGE-D, and necdin. Comparison of the structure of members of MAGE superfamily points to the existence of a domain organization of these proteins. The central, core domain (second domain) is highly conservative. The first domain is homologous among MAGE family members with a CT expression, but unique for each member of the MAGE-D and necdin families. In addition to the homology of the central domain, the third domain is also homologous among all members of MAGE superfamily, but to a much lesser extent. The MAGE-D proteins contain an additional, fourth domain, which in the case of MAGE-D3 coincides with trophinin, a separate molecule described previously as an adhesion molecule that participates in embryo implantation. The structural classification of the members of MAGE superfamily might help in the future to understand the biological function of MAGE proteins. One important property of the CT antigens is the up-regulation of their expression by DNA ***demethylating*** agents, indicating a possible mechanism for their re-expression in tumors. One of the implications of this particular property could be that a combination of immunotherapy targeting CT antigens with chemotherapy inducing up-regulation of CT antigens might result in more efficient tumor eradication.

L17 ANSWER 2 OF 2 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
AN 1999:406727 BIOSIS
DN PREV199900406727
TI Expression of GST - pi and Methylation of GST - pi DNA in human gastric cancer.
AU Liang Xiaoqiu (1); Su Qi (1); Yang Hepin (1)
CS (1) Institute of Oncology, Hengyang Medical College, Hengyang China
SO Zhongguo Zhongliu Linchuang, (May 20, 1999) Vol. 26, No. 5, pp. 352-354.
ISSN: 1000-8179.
DT Article
LA Chinese
SL Chinese; English
AB Objective: To study the relationship between the expression of GST - pi and methylation status of GST - pi gene in gastric cancers. Methods: The GST - pi was detected in 116 human gastric cancers and 53 precancerous lesions with S - P immunohistochemical method using GST - pi monoclonal antibody. The methylation status of the 5' end regulatory sequence CCGG site of GST - pi gene was also investigated by means of restriction endonuclease analysis, PCR and Southern blotting methods in 14 human gastric cancers and normal gastric mucosa. Results: The positive rate of GST - pi in normal gastric mucosa, intestinal metaplasia, atypical hyperplasia and gastric cancer were 10% (4/39), 76% (19/25), 89% (25/28), 77% (89/116) respectively. The positive rate in gastric cancer and precancerous lesions were markedly higher than that of the normal gastric mucosa ($P < 0.01$). As compared with that of the normal gastric mucosa, the GST - pi DNA of gastric cancer was markedly ***hypomethylated*** ($P < 0.01$). A close correlation existed between overexpression of GST - pi and ***hypomethylation*** of GST - pi DNA in gastric cancer ($P < 0.05$). Conclusion: GST - pi is probably involved in the carcinogenesis and development of gastric cancer, and is a ***tumor*** ***associated*** ***antigen*** of gastric cancer. ***Hypomethylation*** of GST - pi gene might be a molecular factor responsible for overexpression of GST - pi.

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(FILE 'HOME' ENTERED AT 14:18:30 ON 11 APR 2002)

FILE 'BIOSIS, MEDLINE, EMBASE' ENTERED AT 14:18:37 ON 11 APR 2002
E DE SANTIS/AU
L1 224 S DE SANTIS R/AU
L2 13 S DE SANTIS RITA/AU
L3 43464 S ANTIGEN PRESENTING CELL? OR APC
L4 27249 S HYPOMETHYLAT? OR DEMETHYLAT? OR UNMETHYLAT?
L5 52 S L3 (S) L4
L6 24 DUP REM L5 (28 DUPLICATES REMOVED)
L7 3494 S CANCER TESTIS ANTIGEN? OR CTA
L8 94 S L7 AND REVIEW
L9 64 DUP REM L8 (30 DUPLICATES REMOVED)
L10 152 S CANCER TESTIS ANTIGEN?
L11 7 S L10 AND REVIEW
L12 5 DUP REM L11 (2 DUPLICATES REMOVED)
L13 10042 S CANCER ASSOCIATED ANTIGEN? OR TUMOR ASSOCIATED ANTIGEN?
L14 24 S L7 AND L4
L15 11 DUP REM L14 (13 DUPLICATES REMOVED)
L16 4 S L13 AND L4
L17 2 DUP REM L16 (2 DUPLICATES REMOVED)

=> l13 and review
L13 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter "HELP COMMANDS" at an arrow prompt (=>).

=> s l1 and review
L18 3 L1 AND REVIEW

=> dup rem l18
PROCESSING COMPLETED FOR L18
L19 3 DUP REM L18 (0 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 3 ANSWERS - CONTINUE? Y/(N):y

L19 ANSWER 1 OF 3 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 93137462 EMBASE
DN 1993137462
TI [Maintenance treatment of inactive Crohn's disease].
LA TERAPIA DI MANTENIMENTO NELLA MALATTIA DI CROHN INATTIVA.
AU Zannoni F.; ***De Santis R.*** ; Testa C.; Prantera C.
CS Divisione di Gastroenterologia, Ospedale Nuovo Regina Margherita, Via Morosini 30,00153 Roma, Italy
SO Argomenti di Gastroenterologia Clinica, (1992) 5/SUPPL. 1 (35-41).
ISSN: 1120-8651 CODEN: AGCLEN
CY Italy
DT Journal; General Review
FS 048 Gastroenterology
030 Pharmacology
037 Drug Literature Index
LA Italian
SL English; Italian

L19 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1989:146575 BIOSIS
DN BR36:68616
TI THE PATHWAY OF SPERM-EGG INTERACTION IN ASCIDIANS BIOLOGY AND CHEMISTRY.
AU ***DE SANTIS R*** ; PINTO M R
CS DEP. CELL DEV. BIOL., STAZIONE ZOOLOGICA DE NAPOLI, VILLA COMUNALE, 80121

NAPOLI, ITALY.
SO Zool. Sci., (1988) 5 (5), 919-924.
CODEN: ZOSCEX. ISSN: 0289-0003.
FS BR; OLD
LA English

L19 ANSWER 3 OF 3 MEDLINE
AN 60223861 MEDLINE
DN 60223861
TI The complementary power of serum in liver disease (Critical ***review*** and clinical contribution).
AU IPPOLITO A; MANNO G; CICCONETTI G; ***DE SANTIS R***
SO Rass Fisiopat Clin Ter, (1959 Nov) 31 986-1002.
DT Journal
LA Italian
FS OLDMEDLINE
EM 196012
ED Entered STN: 19990716
Last Updated on STN: 19990716

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(FILE 'HOME' ENTERED AT 14:18:30 ON 11 APR 2002)

FILE 'BIOSIS, MEDLINE, EMBASE' ENTERED AT 14:18:37 ON 11 APR 2002
E DE SANTIS/AU
L1 224 S DE SANTIS R/AU
L2 13 S DE SANTIS RITA/AU
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L5 52 S L3 (S) L4
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L8 94 S L7 AND REVIEW
L9 64 DUP REM L8 (30 DUPLICATES REMOVED)
L10 152 S CANCER TESTIS ANTIGEN?
L11 7 S L10 AND REVIEW
L12 5 DUP REM L11 (2 DUPLICATES REMOVED)
L13 10042 S CANCER ASSOCIATED ANTIGEN? OR TUMOR ASSOCIATED ANTIGEN?
L14 24 S L7 AND L4
L15 11 DUP REM L14 (13 DUPLICATES REMOVED)
L16 4 S L13 AND L4
L17 2 DUP REM L16 (2 DUPLICATES REMOVED)
L18 3 S L1 AND REVIEW
L19 3 DUP REM L18 (0 DUPLICATES REMOVED)

=> s l13 and review
L20 460 L13 AND REVIEW

=> dup rem l20
PROCESSING COMPLETED FOR L20
L21 349 DUP REM L20 (111 DUPLICATES REMOVED)

=> d bib abs 1-10

L21 ANSWER 1 OF 349 MEDLINE
AN 2002165479 IN-PROCESS
DN 21895504 PubMed ID: 11897572
TI Immunotherapy of human papillomavirus-associated malignancies and the challenges posed by T-cell tolerance.
AU Wilcox Ryan A; Chen Lieping
CS Department of Immunology, Mayo Clinic, Rochester, MN 55905.
SO FRONTIERS IN BIOSCIENCE, (2002 Apr 1) 7 D853-71.
Journal code: 9702166. ISSN: 1093-4715.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20020319
Last Updated on STN: 20020319
AB Human papillomaviruses are associated with a broad range of carcinomas, including cervical cancer. Although the delivery of immunogenic ***tumor*** - ***associated*** ***antigens*** represents a promising approach in the treatment of these malignancies, the imposition of T cell tolerance poses a significant challenge in this endeavor. The purpose of this ***review*** is to discuss T cell tolerance and the role of T cell costimulation in the immunotherapy of HPV-associated malignancies.

L21 ANSWER 2 OF 349 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2002065774 EMBASE
TI Telomerase as a universal ***tumor*** - ***associated*** ***antigen*** for cancer immunotherapy.
AU Vonderheide R.H.
CS R.H. Vonderheide, Univ. of Pennsylvania Sch. of Med., Abramson Family Can. Res. Institute, 421 Curie Blvd., Philadelphia, PA 19104, United States
SO Oncogene, (21 Jan 2002) 21/4 REV. ISS. 1 (674-679).
Refs: 47
ISSN: 0950-9232 CODEN: ONCNES
CY United Kingdom
DT Journal; General Review
FS 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Although the search for pharmacologic inhibitors of telomerase activity represents a promising approach for telomerase-based anti-cancer therapy, the immunological properties of the telomerase reverse transcriptase hTERT suggest that the enzyme is also an attractive target for novel immunotherapies against cancer. Data from both human and murine systems demonstrate that cytotoxic T-lymphocytes (CTL) can recognize peptides derived from TERT and kill TERT-positive tumor cells of multiple histologies. Given the vast overexpression of hTERT in human tumors and its low-level expression in rare normal tissues, clinical trials have begun that test the credentials of hTERT as a broadly applicable target for immunotherapy of cancer.

L21 ANSWER 3 OF 349 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2002106544 EMBASE
TI Influence of tumor vaccines on graft versus tumor activity and graft versus host disease in allogeneic bone marrow transplantation.
AU Mullen C.A.
CS C.A. Mullen, Department of Pediatrics, University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, United States. cmullen@mail.mdanderson.org
SO Leukemia and Lymphoma, (2002) 43/3 (503-510).
Refs: 35
ISSN: 1042-8194 CODEN: LELYEA
CY United Kingdom
DT Journal; General Review
FS 016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Powerful immunologically-mediated antitumor efforts can be observed in allogeneic hematopoietic stem cell transplantation. In the absence of specific immune interventions, this graft versus tumor effect is closely associated with graft versus host disease. In the work summarized here, the influence of cellular tumor vaccines on graft versus tumor activity and graft versus host disease is examined in a murine model of MHC-matched, minor histocompatibility antigen-mismatched bone marrow transplantation. The experiments have generated the following conclusions. First, complex cellular vaccines, which include recipient minor histocompatibility antigens, when administered to allogeneic donors generate powerful graft versus tumor effects but also induce unacceptable exacerbations of graft versus host disease. Second, cellular tumor vaccines, which contain recipient minor histocompatibility antigens, can be administered to transplant recipients after transplant without significant exacerbation of GVHD and with retention of clinically significant graft versus tumor effects. Third, immunization of donors with molecularly defined ***tumor*** - ***associated*** ***antigens*** , which are not recipient minor histocompatibility antigens, can be coupled with post-transplant immunization of recipients with cellular vaccines without exacerbation of GVHD.

L21 ANSWER 4 OF 349 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
1
AN 2002:182271 BIOSIS
DN PREV200200182271
TI Immunotherapy for nonmelanoma skin cancer: Does it have a future.
AU Urosevic, Mirjana; Dummer, Reinhard (1)
CS (1) Department of Dermatology, University Hospital of Zurich, Gloriastrasse 31, CH-8091, Zurich: dummer@derm.unizh.ch Switzerland
SO Cancer, (January 15, 2002) Vol. 94, No. 2, pp. 477-485. print.
ISSN: 0008-543X.
DT Article
LA English
AB BACKGROUND: Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)
of the skin are the most common malignancies in the white human population, accounting for greater than 95% of nonmelanoma skin cancers (NMSCs). Current data show an increasing incidence of NMSC in recent decades. Although the mortality is low, this cancer group is associated with substantial morbidity. Multiple treatment modalities are available for NMSC, with surgery being a "corner-stone" of current therapy approaches. However, in patients with multiple lesions or in cases of tumors on critical locations, disfigurement and the disease recurrence may represent a serious problem associated with the surgical treatment. The purpose of this study was to ***review*** and analyze whether NMSC could represent a target for immune therapy, evaluating the aspects of the availability of tumor antigens and the existence of tumor specific immune response, including a summary of the major clinical studies dealing with immunotherapy for NMSC. METHODS: The authors have reviewed the available
medical literature on NMSC, with a focus on tumor immunology and associated abnormalities, as well as immunotherapy-based treatment trials. RESULTS: The major advantage of NMSCs is that they arise from the skin, which makes them easily detectable and treatable. Furthermore, these tumors posses all the prerequisites, i.e., the presence of ***tumor***

- ***associated*** ***antigens*** as well as the tumor specific immune response, needed for immune intervention. This also was confirmed in various studies demonstrating clinical efficacy of cytokines and other immune response modifiers. CONCLUSIONS: In addition to clinical cure, by activating and stimulating patient's immune resources this therapeutic option may be a "silver bullet," providing a long-term protective immunity against initial tumor.

L21 ANSWER 5 OF 349 MEDLINE
AN 2002177021 IN-PROCESS
DN 21906712 PubMed ID: 11910045
TI The Potential of DNA Vaccination against ***Tumor*** - ***Associated*** ***Antigens*** for Antitumor Therapy.
AU Haupt Katharina; Roggendorf Michael; Mann Klauss
CS Division of Clinical Chemistry, Department of Internal Medicine, Institute for Virology, and Division of Endocrinology, Department of Internal Medicine, University of Essen, 45122 Essen, Germany.
SO Exp Biol Med (Maywood), (2002 Apr) 227 (4) 227-37.
Journal code: 100973463. ISSN: 1535-3702.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20020324
Last Updated on STN: 20020324
AB Conventional treatment approaches for malignant tumors are highly invasive and sometimes have only a palliative effect. Therefore, there is an increasing demand to develop novel, more efficient treatment options. Increased efforts have been made to apply immunomodulatory strategies in antitumor treatment. In recent years, immunizations with naked plasmid DNA encoding ***tumor*** - ***associated*** ***antigens*** have revealed a number of advantages. By DNA vaccination, antigen-specific cellular as well as humoral immune reponses can be generated. The induction of specific immune responses directed against antigens expressed in tumor cells and displayed e.g., by MHC class I complexes can inhibit tumor growth and lead to tumor rejection. The improvement of vaccine efficacy has become a critical goal in the development of DNA vaccination as antitumor therapy. The use of different DNA delivery techniques and coadministration of adjuvants including cytokine genes may influence the pattern of specific immune responses induced. This brief ***review*** describes recent developments to optimize DNA vaccination against ***tumor*** - ***associated*** ***antigens*** . The prerequisite for a successful antitumor vaccination is breaking tolerance to ***tumor*** - ***associated*** ***antigens*** , which represent "self-antigens." Currently, immunization with xenogeneic DNA to induce immune responses against self-molecules is under intensive investigation. Tumor cells can develop immune escape mechanisms by generation of antigen loss variants, therefore, it may be necessary that DNA vaccines contain more than one tumor antigen. Polyimmunization with a mixture of ***tumor*** - ***associated*** ***antigen*** genes may have a synergistic effect in tumor treatment. The identification of tumor antigens that may serve as targets for DNA immunization has proceeded rapidly. Preclinical studies in animal models are promising that DNA immunization is a potent strategy for mediating antitumor effects in vivo. Thus, DNA vaccines may offer a novel treatment for tumor patients. DNA vaccines may also be useful in the prevention of tumors with genetic predisposition. By DNA vaccination preventing infections, the development of viral-induced tumors may be avoided.

L21 ANSWER 6 OF 349 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2002093017 EMBASE
TI Cancer/testis antigens: Structural and immunobiological properties.
AU Kirkin A.F.; Dzhandzhugazyan K.N.; Zeuthen J.
CS Dr. J. Zeuthen, Department of Tumor Cell Biology, Institute of Cancer Biology, Danish Cancer Society, Strandboulevarden 49, DK-2100 Copenhagen, Denmark. jz@cancer.dk
SO Cancer Investigation, (2002) 20/2 (222-236).
Refs: 106
ISSN: 0735-7907 CODEN: CINVD7
CY United States
DT Journal; General Review
FS 016 Cancer
026 Immunology, Serology and Transplantation
028 Urology and Nephrology
LA English
SL English
AB Characterization of ***tumor*** - ***associated*** ***antigens*** recognized by cytotoxic T lymphocytes which has evolved during recent years opens new possibilities for specific anti-cancer immunotherapy. Among different groups of ***tumor*** - ***associated*** ***antigens*** , cancer/testis (CT) antigens (expressed in many tumors and among normal tissues only in testes) represent the most perspective antigens for immunotherapy because of their broad tumor-specific expression. More than 50 CT antigens have been described so far and, for many of them, epitopes recognized by T lymphocytes have been identified. The most studied group of CT antigens is the MAGE proteins, which form the so-called MAGE superfamily, together with some MAGE-like proteins that have a different distribution than classical CT antigens. The MAGE superfamily includes five families: MAGE-A, MAGE-B, MAGE-C, MAGE-D, and necdin. Comparison of the structure of members of MAGE superfamily points to the existence of a domain organization of these proteins. The central, core domain (second domain) is highly conservative. The first domain is homologous among MAGE family members with a CT expression, but unique for each member of the MAGE-D and necdin families. In addition to the homology of the central domain, the third domain is also homologous among all members of MAGE superfamily, but to a much lesser extent. The MAGE-D proteins contain an additional, fourth domain, which in the case of MAGE-D3 coincides with trophinin, a separate molecule described previously as an adhesion molecule that participates in embryo implantation. The structural classification of the members of MAGE superfamily might help in the future to understand the biological function of MAGE proteins. One important property of the CT antigens is the up-regulation of their expression by DNA demethylating agents, indicating a possible mechanism for their reexpression in tumors. One of the implications of this particular property could be that a combination of immunotherapy targeting CT antigens with chemotherapy inducing up-regulation of CT antigens might result in more efficient tumor eradication.

L21 ANSWER 7 OF 349 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2002085728 EMBASE
TI Prophylactic cancer vaccines.
AU Finn O.J.; Forni G.
CS O.J. Finn, Univ. of Pittsburgh Sch. of Medicine, Univ. of Pittsburgh Cancer Institute, W1142 Biomedical Science Tower, Pittsburgh, PA 15261, United States. ojfinn@pitt.edu
SO Current Opinion in Immunology, (1 Apr 2002) 14/2 (172-177).
Refs: 68
ISSN: 0952-7915 CODEN: COPIEL
CY United Kingdom
DT Journal; General Review
FS 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Increasingly, data from distinct experimental systems show that immunity can be activated to prevent tumors. The rationale for prevention is strong because, in that setting, one deals with an immune system that is neither impaired by tumor- and treatment-induced suppression nor tolerant to ***tumor*** - ***associated*** ***antigens*** that have been encountered in the absence of correct presentation and costimulatory/danger signals. The use of overexpressed or mutated proteins, or mutated oncogenic growth factor receptors, as ***tumor*** - ***associated*** ***antigens*** yields rational targets for specific immunoprevention. Transgenic mouse models are providing encouraging indications of future usefulness of vaccines that are based on these molecules.

L21 ANSWER 8 OF 349 MEDLINE DUPLICATE 2
AN 2002060439 MEDLINE
DN 21643710 PubMed ID: 11784252
TI Micrometastatic tumor detection in patients with head and neck cancer: a preliminary report.
AU Wirtschafter Ari; Benninger Michael S; Moss Thomas J; Umiel Tehila; Blazoff Kathleen; Worsham Maria J
CS Department of Otolaryngology-Head and Neck Surgery, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202, USA.
SO ARCHIVES OF OTOLARYNGOLOGY -- HEAD AND NECK SURGERY, (2002 Jan) 128 (1)
40-3.
Journal code: 8603209. ISSN: 0886-4470.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200201
ED Entered STN: 20020125
Last Updated on STN: 20020128
Entered Medline: 20020124
AB OBJECTIVE: To apply a new immunocytochemistry (ICC) assay to peripheral blood samples for micrometastatic circulating tumor cell detection in patients with head and neck squamous cell cancer (HNSCC). DESIGN: The ICC assay uses established monoclonal antibodies that bind to ***tumor*** - ***associated*** ***antigens*** combined with an enrichment system that uses positive selection with anti-human epithelial antigen (EpCAM antibody) to detect circulating tumor cells. SUBJECTS: Eighteen consecutive patients newly diagnosed as having HNSCC are described. RESULTS: Of the 18 patients, 8 (44%) demonstrated circulating tumor cells using the ICC assay. The numbers of patients positive for circulating tumor cells per stage are as follows: stage I, 1 of 1; stage II, 0 of 2; stage III, 2 of 5; stage IV, 5 of 6; and unknown stage, 0 of 4. The numbers of patients positive for circulating tumor cells per location are as follows: oral cavity, 1 of 2; oropharynx, 3 of 4; glottic area, 3 of 5; supraglottic area, 1 of 3; and unknown primary 0 of 4. CONCLUSIONS: Circulating tumor cells were identified in almost half of the patients using the ICC assay. In a literature ***review*** , we were not able to identify previous reports of circulating tumor cell detection in patients with HNSCC from peripheral blood samples using ICC or identify any study that has attempted to quantify circulating tumor cell levels. Although the clinical implications of circulating tumor cells in micrometastatic tumor detection in patients with HNSCC are still unknown, they may be significant. Long-term follow-up may help elucidate the patients in whom conventional treatment may fail and, thus, those who may benefit from different treatment; it may also assist with the detection of recurrence

with a simple blood collection.

L21 ANSWER 9 OF 349 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2001151596 EMBASE
TI Cancer vaccines.
AU Moingeon P.
CS P. Moingeon, Aventis Pasteur, Campus Merieux, 1541 Avenue Marcel Merieux,
69280 Marcy l'Etoile, France. philippe.moingeon@aventis.com
SO Vaccine, (8 Jan 2001) 19/11-12 (1305-1326).
Refs: 164
ISSN: 0264-410X CODEN: VACCDE
PUI S 0264-410X(00)00372-8
CY United Kingdom
DT Journal; General Review
FS 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB Cancer vaccines have been extensively tested in animal models, and in humans. Initial studies focused on first generation vaccines based on whole cell preparations or tumor lysates derived from autologous or allogeneic tumors. Clinical studies conducted with such candidate vaccines contributed to establish the feasibility of immunizing cancer patients against their own tumors. Significant clinical benefits were observed, both in terms of long term survival and recurrence rate, in some of these trials. More recently, however, cancer vaccines targeting well-characterized ***tumor*** - ***associated*** ***antigens*** , i.e. molecules selectively or preferentially expressed by cancer cells but not by normal cells, have been designed and tested in humans. Results obtained as of today with these second-generation vaccines suggest that they are safe and that they can elicit humoral and cellular responses against tumor-specific antigens, without inducing unacceptable clinical signs of autoimmunity. Advances in tumor biology and tumor immunity have helped to better understand the mechanisms displayed by a number of tumors to escape host immunity. This bulk of new knowledge will be used to design future cancer vaccines, which will likely target multiple TAAs, presented by different antigen presentation platforms, in association with synthetic adjuvants and/or immunostimulatory cytokines. Lastly, specific tools allowing to assess in a qualitative and quantitative manner immune responses are critically needed in order to establish correlates between clinical and immune responses in patients receiving experimental vaccines. .COPYRGT. 2001 Elsevier Science Ltd.

L21 ANSWER 10 OF 349 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 3
AN 2001:558177 BIOSIS
DN PREV200100558177
TI Dendritic cells in cancer vaccines.
AU Brossart, Peter (1); Wirths, Stefan; Brugger, Wolfram; Kanz, Lothar
CS (1) Department of Hematology, Oncology and Immunology, University of Tuebingen, Otfried-Mueller-Strasse-10, D-72076, Tuebingen: peter.brossart@med.uni-tuebingen.de Germany
SO Experimental Hematology (Charlottesville), (November, 2001) Vol. 29, No. 11, pp. 1247-1255. print.
ISSN: 0301-472X.
DT Article
LA English
SL English
AB Dendritic cells (DC) are recognized as the most potent antigen-presenting cells with the ability to stimulate naive resting T cells and to initiate primary immune responses. Encouraging results in vaccination studies in animal models and the development of protocols to generate sufficient numbers of human DC for clinical application have led to attempts to verify the feasibility and efficacy of this approach in patients in the context of Phase I/II vaccination trials. This ***review*** aims to present a concise overview of the current knowledge in DC development and biology and describes the recent data of the first published DC-based vaccination studies. These preliminary trials indicate the immunotherapies utilizing DC-presenting ***tumor*** - ***associated*** ***antigens*** can safely be administered to patients with cancer and induce significant immunologic and clinical responses.

=> d his

(FILE 'HOME' ENTERED AT 14:18:30 ON 11 APR 2002)

FILE 'BIOSIS, MEDLINE, EMBASE' ENTERED AT 14:18:37 ON 11 APR 2002
E DE SANTIS/AU
L1 224 S DE SANTIS R/AU
L2 13 S DE SANTIS RITA/AU
L3 43464 S ANTIGEN PRESENTING CELL? OR APC
L4 27249 S HYPOMETHYLAT? OR DEMETHYLAT? OR UNMETHYLAT?
L5 52 S L3 (S) L4
L6 24 DUP REM L5 (28 DUPLICATES REMOVED)
L7 3494 S CANCER TESTIS ANTIGEN? OR CTA
L8 94 S L7 AND REVIEW
L9 64 DUP REM L8 (30 DUPLICATES REMOVED)
L10 152 S CANCER TESTIS ANTIGEN?
L11 7 S L10 AND REVIEW
L12 5 DUP REM L11 (2 DUPLICATES REMOVED)
L13 10042 S CANCER ASSOCIATED ANTIGEN? OR TUMOR ASSOCIATED ANTIGEN?
L14 24 S L7 AND L4
L15 11 DUP REM L14 (13 DUPLICATES REMOVED)
L16 4 S L13 AND L4
L17 2 DUP REM L16 (2 DUPLICATES REMOVED)
L18 3 S L1 AND REVIEW
L19 3 DUP REM L18 (0 DUPLICATES REMOVED)
L20 460 S L13 AND REVIEW
L21 349 DUP REM L20 (111 DUPLICATES REMOVED)

=> s dendritic cell? and l4 and ex vivo expan?
L22 0 DENDRITIC CELL? AND L4 AND EX VIVO EXPAN?

=> s l4 and (dendritic cell? or macrophage? or monocy? or antigen presenting cell? or apc)
1 FILES SEARCHED...
L23 412 L4 AND (DENDRITIC CELL? OR MACROPHAGE? OR MONOCY? OR ANTIGEN PRESENTING CELL? OR APC)

=> s ex vivo expan? and l23
L24 0 EX VIVO EXPAN? AND L23

=> s ex vivo and l23
L25 0 EX VIVO AND L23

=> s activa? and l23
L26 195 ACTIVA? AND L23

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PROCESSING COMPLETED FOR L26
L27 102 DUP REM L26 (93 DUPLICATES REMOVED)

=> d bib abs 1-10

L27 ANSWER 1 OF 102 MEDLINE
AN 2002148881 IN-PROCESS
DN 21849646 PubMed ID: 11861616
TI CpG motifs in bacterial DNA and their immune effects.
AU Krieg Arthur M
CS Department of Veterans Affairs Medical Center, Iowa City, Iowa 52246.
SO ANNUAL REVIEW OF IMMUNOLOGY, (2002) 20 709-60.
Journal code: 8309206. ISSN: 0732-0582.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20020308
Last Updated on STN: 20020308
AB ***Unmethylated*** CpG motifs are prevalent in bacterial but not vertebrate genomic DNAs. Oligodeoxynucleotides (ODN) containing CpG motifs ***activate*** host defense mechanisms leading to innate and acquired immune responses. The recognition of CpG motifs requires Toll-like receptor (TLR) 9, which triggers alterations in cellular redox balance and the induction of cell signaling pathways including the mitogen ***activated*** protein kinases (MAPKs) and NFkappaB. Cells that express TLR-9, which include plasmacytoid ***dendritic*** ***cells*** (PDCs) and B cells, produce Th1-like proinflammatory cytokines, interferons, and chemokines. Certain CpG motifs (CpG-A) are especially potent at ***activating*** NK cells and inducing IFN-alpha production by PDCs, while other motifs (CpG-B) are especially potent B cell ***activators*** . CpG-induced ***activation*** of innate immunity protects against lethal challenge with a wide variety of pathogens, and has therapeutic activity in murine models of cancer and allergy. CpG ODN also enhance the development of acquired immune responses for prophylactic and therapeutic vaccination.

L27 ANSWER 2 OF 102 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
1
AN 2002:210041 BIOSIS
DN PREV200200210041
TI CpG oligonucleotides: Novel regulators of osteoclast differentiation.
AU Zou, Wei; Schwartz, Harry; Endres, Stefan; Hartmann, Gunther; Bar-Shavit, Zvi (1)
CS (1) The H. Hubert Humphrey Center for Experimental Medicine and Cancer Research, The Hebrew University Faculty of Medicine, Jerusalem, 91120: barsha@cc.huji.ac.il Israel
SO FASEB Journal, (March, 2002) Vol. 16, No. 3, pp. 274-282. http://www.fasebj.org/. print.
ISSN: 0892-6638.
DT Article
LA English
AB The ***macrophage*** capability to recognize bacterial DNA is mimicked by oligodeoxynucleotides containing ***unmethylated*** CG dinucleotides ('CpG' motifs) in specific sequence contexts (CpG ODN). CpG ODN stimulates NF-kappaB ***activation*** in murine ***macrophages*** . In light of the pivotal role played by NF-kappaB in osteoclast differentiation, we examined the ability of CpG ODN to modulate osteoclastogenesis. CpG ODN alone induced TRAP-positive cells in bone marrow ***macrophage*** (BMM) cultures, but not multinucleation or

calcitonin receptor expression. CpG ODN inhibited RANKL-induced osteoclastogenesis when present from the beginning of BMM culture, but strongly increased RANKL-induced osteoclastogenesis in RANKL-pretreated BMMs. CpG ODN enhanced the expression of interleukin 1beta (IL-1beta) and tumor necrosis factor alpha (TNF-alpha). Antibodies to TNF-alpha and the TNF type 1 receptor, but not the addition of IL-1 receptor antagonist, blocked CpG ODN-induced osteoclastogenesis in RANKL-pretreated cultures. On the other hand, CpG ODN reduced expression of the M-CSF receptor, which is critical during the initiation of osteoclast differentiation. These results suggest that CpG ODN, via the induction of TNF-alpha, support osteoclastogenesis in cells that are committed to the osteoclast differentiation pathway but, due to down-modulation of M-CSF receptor, inhibit early steps of osteoclast differentiation. Thus, CpG ODN represents a potential therapeutic tool for treating bone diseases.

L27 ANSWER 3 OF 102 MEDLINE DUPLICATE 2
AN 2002046466 MEDLINE
DN 21623866 PubMed ID: 11751945
TI Immunostimulatory DNA sequences influence the course of adjuvant arthritis.
AU Ronaghy Arash; Prakken Berent J; Takabayashi Kenji; Firestein Gary S; Boyle David; Zvailfler Nathan J; Roord Sarah T A; Albani Salvatore; Carson Dennis A; Raz Eyal
CS Department of Medicine, Division of Rheumatology, Allergy and Immunology, University of California at San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA.
NC AI 40682 (NIAID)
AR 07567 (NIAMS)
AR 44850 (NIAMS)
AR 45347 (NIAMS)
SO JOURNAL OF IMMUNOLOGY, (2002 Jan 1) 168 (1) 51-6.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200201
ED Entered STN: 20020124
Last Updated on STN: 20020125
Entered Medline: 20020111
AB Bacterial DNA is enriched in ***unmethylated*** CpG motifs that have been shown to ***activate*** the innate immune system. These immunostimulatory DNA sequences (ISS) induce inflammation when injected directly into joints. However, the role of bacterial DNA in systemic arthritis is not known. The purpose of the present experiments was to determine whether ISS contributes to the development of adjuvant arthritis in Lewis rats after intradermal injection of heat-killed Mycobacterium tuberculosis (Mtb). The results showed that Mtb DNA was necessary for maximal joint inflammation in adjuvant arthritis but could be replaced by synthetic ISS oligodeoxynucleotides. The arthritis-promoting effect of the Mtb DNA or of the ISS oligodeoxynucleotides correlated with an increased Th1 response to Mtb Ags, as measured by the production of IFN-gamma and increased production of the osteoclast differentiation factor, receptor ***activator*** of NF-kappaB ligand (RANKL). The Mtb DNA did not enter the joints but dispersed to the bone marrow and spleen before the onset of systemic joint inflammation. Thus, adjuvant arthritis is a microbial DNA-dependent disease. In this model, we postulate that massive and prolonged ***activation*** of ***macrophages*** , ***dendritic*** ***cells*** , and osteoclast precursors in the bone marrow may prime the joints for the induction of inflammatory Th1 immune responses to Mtb Ags.

L27 ANSWER 4 OF 102 MEDLINE
AN 2001454809 MEDLINE
DN 21391782 PubMed ID: 11500395
TI Potent stimulation of the innate immune system by a Leishmania brasiliensis recombinant protein.
AU Borges M M; Campos-Neto A; Sleath P; Grabstein K H; Morrissey P J; Skeiky Y A; Reed S G
CS Instituto Butantan, Sao Paulo, Brazil.
NC AI25038 (NIAID)
SO INFECTION AND IMMUNITY, (2001 Sep) 69 (9) 5270-7.
Journal code: GO7; 0246127. ISSN: 0019-9567.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200109
ED Entered STN: 20010814
Last Updated on STN: 20010917
Entered Medline: 20010913
AB The interaction of the innate immune system with the microbial world involves primarily two sets of molecules generally known as microbial pattern recognition receptors and microbial pattern recognition molecules, respectively. Examples of the former are the Toll receptors present particularly in ***macrophages*** and ***dendritic*** ***cells*** . Conversely, the microbial pattern recognition molecules are conserved protist homopolymers, such as bacterial lipopolysaccharides, lipoteichoic acids, peptidoglycans, glucans, mannans, ***unmethylated*** bacterial DNA, and double-strand viral RNA. However, for protists that lack most of these molecules, such as protozoans, the innate immune system must have evolved receptors that recognize other groups of microbial molecules. Here we present evidence that a highly purified protein encoded by a Leishmania brasiliensis gene may be one such molecule. This recombinant leishmanial molecule, a homologue of eukaryotic ribosomal elongation and initiation factor 4a (LeIF), strongly stimulates spleen cells from severe combined immunodeficient (SCID) mice to produce interleukin-12 (IL-12), IL-18, and high levels of gamma interferon. In addition, LeIF potentiates the cytotoxic activity of the NK cells of these animals. Because LeIF is a conserved molecule and because SCID mice lack T and B lymphocytes but have a normal innate immune system (normal reticuloendothelial system and NK cells), these results suggest that proteins may also be included as microbial pattern recognition molecules. The nature of the receptor involved in this innate recognition is unknown. However, it is possible to exclude the Toll receptor Tlr4 as a putative LeIF receptor because the gene encoding this receptor is defective in C3H/HeJ mice, the mouse strain used in the present studies.

L27 ANSWER 5 OF 102 MEDLINE DUPLICATE 3
AN 2001544765 MEDLINE
DN 21475889 PubMed ID: 11591791
TI Intracisternally localized bacterial DNA containing CpG motifs induces meningitis.
AU Deng G M; Liu Z Q; Tarkowski A
CS Department of Rheumatology, Goteborg University, Goteborg, Sweden.. guo-min@rheuma.gu.se
SO JOURNAL OF IMMUNOLOGY, (2001 Oct 15) 167 (8) 4616-26.
Journal code: 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200112
ED Entered STN: 20011010
Last Updated on STN: 20020122
Entered Medline: 20011207
AB ***Unmethylated*** CpG motifs are frequently found in bacterial DNA, and have recently been shown to exert immunostimulatory effects on leukocytes. Since bacterial infections in the CNS will lead to local release of prokaryotic DNA, we wanted to investigate whether such an event might trigger meningitis. To that end, we have intracisternally injected mice and rats with bacterial DNA and oligonucleotides containing CpG motifs. Histopathological signs of meningitis were evident within 12 h and lasted for at least 14 days, and were characterized by an influx of ***monocytic*** , Mac-3(+) cells and by a lack of T lymphocytes. To study the mechanisms whereby ***unmethylated*** CpG DNA gives rise to meningitis, we deleted the ***monocyte*** / ***macrophage*** population leading to abrogation of brain inflammation. Also, interaction with NF-kappaB using antisense technology led to down-regulation of proinflammatory cytokine production and frequency of meningitis. Furthermore, specific interactions with vascular selectin expression and inhibition of NO synthase led to a significant amelioration of meningitis, altogether indicating that this condition is dependent on ***macrophages*** and their products. In contrast, neutrophils, NK cells, T/B lymphocytes, IL-12, and complement system were not instrumental in meningitis triggered by bacterial DNA containing CpG motifs. This study proves that bacterial DNA containing ***unmethylated*** CpG motifs induces meningitis, and indicates that this condition is mediated in vivo by ***activated*** ***macrophages*** .

L27 ANSWER 6 OF 102 MEDLINE DUPLICATE 4
AN 2001539706 MEDLINE
DN 21453771 PubMed ID: 11568631
TI ***Activation*** of microglia and astrocytes by CpG oligodeoxynucleotides.
AU Takeshita S; Takeshita F; Haddad D E; Janabi N; Klinman D M
CS Section of Retroviral Immunology, Bldg 29A, Rm 3 D 10, Center for Biologics and Evaluation Research, Food and Drug Administration, Bethesda, MD 20892, USA.
SO NEUROREPORT, (2001 Oct 8) 12 (14) 3029-32.
Journal code: 9100935. ISSN: 0959-4965.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200112
ED Entered STN: 20011008
Last Updated on STN: 20020122
Entered Medline: 20011204
AB Bacterial DNA and synthetic oligodeoxynucleotides (ODN) containing ***unmethylated*** CpG motifs stimulate cells of the immune system to secrete a variety of cytokines and chemokines. This function can be carried out by microglia and astrocytes in the CNS. To evaluate the effect of CpG ODN on microglia and astrocytes, purified cells were isolated and cultured in vitro. CpG ODN rapidly up-regulated their production of IL-1beta, IL-6, IL-12, TNFalpha, MIP-1alpha and/or MIP-1beta. In vivo, systemically administered CpG ODN up-regulated the expression of mRNA encoding cytokines and chemokines in normal mouse brain. These findings suggest that CpG ODN can directly ***activate*** immune cells of the CNS.

L27 ANSWER 7 OF 102 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5
AN 2001:210749 BIOSIS
DN PREV200100210749
TI DNA from protozoan parasites Babesia bovis, Trypanosoma cruzi, and T.

brucei is mitogenic for B lymphocytes and stimulates ***macrophage*** expression of interleukin-12, tumor necrosis factor alpha, and nitric oxide.
AU Shoda, Lisl K. M.; Kegerreis, Kimberly A.; Suarez, Carlos E.; Roditi, Isabel; Corral, Ricardo S.; Bertot, Gustavo M.; Norimine, Junzo; Brown, Wendy C. (1)
CS (1) Department of Veterinary Microbiology and Pathology, Washington State University, Pullman, WA, 99164-7040: wbrown@vetmed.wsu.edu USA
SO Infection and Immunity, (April, 2001) Vol. 69, No. 4, pp. 2162-2171. print.
ISSN: 0019-9567.
DT Article
LA English
SL English
AB The ***activation*** of innate immune responses by genomic DNA from bacteria and several nonvertebrate organisms represents a novel mechanism of pathogen recognition. We recently demonstrated the CpG-dependent mitogenic activity of DNA from the protozoan parasite Babesia bovis for bovine B lymphocytes (W. C. Brown, D. M. Estes, S. E. Chantler, K. A. Kegerreis, and C. E. Suarez, Infect. Immun. 66:5423-5432, 1998). However, ***activation*** of ***macrophages*** by DNA from protozoan parasites has not been demonstrated. The present study was therefore conducted to determine whether DNA from the protozan parasites B. bovis, Trypanosoma cruzi, and T. brucei ***activates*** ***macrophages*** to secrete inflammatory mediators associated with protective immunity. DNA from Escherichia coli and all three parasites stimulated B-lymphocyte proliferation and increased ***macrophage*** production of interleukin-12 (IL-12), tumor necrosis factor alpha (TNF-alpha), and nitric oxide (NO). Regulation of IL-12 and NO production occurred at the level of transcription. The amounts of IL-12, TNF-alpha, and NO induced by E. coli and protozoal DNA were strongly correlated (r2 > 0.9) with the frequency of CG dinucleotides in the genome, and immunostimulation by DNA occurred in the order E. coli gtoreq T. cruzi > T. brucei > B. bovis. Induction of inflammatory mediators by E. coli, T. brucei, and B. bovis DNA was dependent on the presence of ***unmethylated*** CpG dinucleotides. However, at high concentrations, E. coli and T. cruzi DNA-mediated ***macrophage*** ***activation*** was not inhibited following methylation. The recognition of protozoal DNA by B lymphocytes and ***macrophages*** may provide an important innate defense mechanism to control parasite replication and promote persistent infection.

L27 ANSWER 8 OF 102 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
6
AN 2001:372834 BIOSIS
DN PREV200100372834
TI Identification of CpG oligonucleotide sequences with high induction of IFN-alpha/beta in plasmacytoid ***dendritic*** ***cells*** .
AU Krug, Anne; Rothenfusser, Simon; Hornung, Veit; Jahrsdoerfer, Bernd; Blackwell, Susan; Ballas, Zuhair K.; Endres, Stefan; Krieg, Arthur M.; Hartmann, Gunther (1)
CS (1) Abteilung fuer Klinische Pharmakologie, Medizinische Klinik Innenstadt, Ziemssenstrasse 1, D-80336, Munich: ghartmann@lrz.uni-muenchen.de Germany
SO European Journal of Immunology, (July, 2001) Vol. 31, No. 7, pp. 2154-2163. print.
ISSN: 0014-2980.
DT Article
LA English
SL English
AB The immature plasmacytoid ***dendritic*** ***cell*** (PDC) is identical with the principal type I IFN-producing cell upon viral infection. Oligodeoxynucleotides which contain ***unmethylated*** CpG motifs (CpG ODN) are recognized by the vertebrate immune system. Previously, we described CpG ODN that strongly ***activate*** human B cells and human blood ***dendritic*** ***cells*** . Here we describe distinct CpG-containing oligonucleotide sequences which, in contrast to previously described CpG ODN, induced high amounts of IFN-alpha and IFN-beta in peripheral blood mononuclear cells (PBMC). Intracellular staining for IFN-alpha revealed that within PBMC CpG ODN-induced IFN-alpha is produced exclusively by PDC. Unlike IFN-alpha, TNF-alpha is up-regulated in PDC by all CpG ODN tested. Purified PDC responded to CpG ODN, demonstrating direct ***activation*** of PDC by CpG ODN. The most active sequence induced the production of up to 5 pg IFN-alpha per single PDC, resulting in more than 400 ng/ml IFN-alpha in the supernatant of PBMC enriched for PDC. The potency of CpG ODN to stimulate IFN-alpha correlated with their ability to stimulate NK cell lytic activity, while purified NK cells did not respond to CpG ODN. IFN-gamma production in PBMC was dependent on CpG ODN-induced IFN-alpha/beta as demonstrated by IFN-alpha/beta blocking antibodies. IFN-alpha-inducing CpG ODN strongly supported IFN-gamma production of TCR-triggered CD4 T cells but were less active than other CpG ODN in stimulating B cells. In conclusion our results demonstrate that particular CpG ODN sequences exist which, due to high IFN-alpha/beta induction in PDC, induce a set of immune responses typical for viral infection.

L27 ANSWER 9 OF 102 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
7
AN 2001:187822 BIOSIS
DN PREV200100187822
TI Interleukin-12- and gamma interferon-dependent protection against malaria conferred by CpG oligodeoxynucleotide in mice.
AU Gramzinski, Robert A.; Doolan, Denise L.; Sedegah, Martha; Davis, Heather L.; Krieg, Arthur M.; Hoffman, Stephen L. (1)
CS (1) Malaria Program, Naval Medical Research Center, 503 Robert Grant Ave., Silver Spring, MD, 20910-7500: hoffmans@nmrc.navy.mil USA
SO Infection and Immunity, (March, 2001) Vol. 69, No. 3, pp. 1643-1649. print.
ISSN: 0019-9567.
DT Article
LA English
SL English
AB ***Unmethylated*** CpG dinucleotides in bacterial DNA or synthetic oligodeoxynucleotides (ODNs) cause B-cell proliferation and immunoglobulin secretion, ***monocyte*** cytokine secretion, and ***activation*** of natural killer (NK) cell lytic activity and gamma interferon (IFN-gamma) secretion in vivo and in vitro. The potent Th1-like immune ***activation*** by CpG ODNs suggests a possible utility for enhancing innate immunity against infectious pathogens. We therefore investigated whether the innate immune response could protect against malaria. Treatment of mice with CpG ODN 1826 (TCCATGACGTTCCTGACGTT, with the CpG dinucleotides underlined) or 1585 (ggGGTCAACGTTGAgggggG, with g representing diester linkages and phosphorothioate linkages being to the right of lowercase letters) in the absence of antigen 1 to 2 days prior to challenge with Plasmodium yoelii sporozoites conferred sterile protection against infection. A higher level of protection was consistently induced by CpG ODN 1826 compared with CpG ODN 1585. The protective effects of both CpG ODNs were dependent on interleukin-12, as well as IFN-gamma. Moreover, CD8+ T cells (but not CD4+ T cells), NK cells, and nitric oxide were implicated in the CpG ODN 1585-induced protection. These data establish that the protective mechanism induced by administration of CpG ODN 1585 in the absence of parasite antigen is similar in nature to the mechanism induced by immunization with radiation-attenuated P. yoelii sporozoites or with plasmid DNA encoding preerythrocytic-stage P. yoelii antigens. We were unable to confirm whether CD8+ T cells, NK cells, or nitric oxide were required for the CpG ODN 1826-induced protection, but this may reflect differences in the potency of the ODNs rather than a real difference in the mechanism of action of the two ODNs. This is the first report that stimulation of the innate immune system by CpG immunostimulatory motifs can confer sterile protection against malaria.

L27 ANSWER 10 OF 102 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 8
AN 2001:147724 BIOSIS
DN PREV200100147724
TI Oligonucleotide containing CpG motifs enhances immune response to mucosally or systemically administered tetanus toxoid.
AU Eastcott, Jean W.; Holmberg, Cynthia J.; Dewhirst, Floyd E.; Esch, Thomas R.; Smith, Daniel J.; Taubman, Martin A. (1)
CS (1) Department of Immunology, Forsyth Institute, 140 Fenway, Boston, MA, 02115: mtaubman@forsyth.org USA
SO Vaccine, (8 February, 2001) Vol. 19, No. 13-14, pp. 1636-1642. print.
ISSN: 0264-410X.
DT Article
LA English
SL English
AB Oligodeoxynucleotides (ODN) containing ***unmethylated*** CpG dinucleotides induce proliferation of B cells and ***activation*** of ***macrophages*** and thus stimulation of the immune system. We tested an oligonucleotide containing an ***unmethylated*** CpG dinucleotide flanked by two 5' purines and two 3' pyrimidines (GAGAACGCTCGACCTTCGAT) for the ability to affect antibody levels to tetanus toxoid (Tt). Groups of male Rowett rats (n = 5-6/group) received colloidal aluminium hydroxide (Al(OH)3) either alone, or with Tt bound to the Al(OH)3, or with Tt bound to Al(OH)3 with the addition of the CpG oligonucleotide. Antigens were administered subcutaneously in the salivary gland vicinity once, or by gastric intubation on 3 consecutive days. On day 124 all animals were given a boost with the same material by the same route. Serum IgG and saliva IgA antibody to Tt was determined by ELISA. Serum antibody levels were significantly higher in ODN + Tt treated rats than in Tt-alone rats immunized by either route after primary or booster immunizations. Thus, administration of an ODN containing ***unmethylated*** CpG motifs along with an immunogen bound to Al(OH)3 can result in enhanced specific antibody when administered by intragastric as well as subcutaneous routes.

=> s l4 (2s) (dendritic cell? or macrophage? or monocy? or antigen presenting cell? or apc)
2 FILES SEARCHED...
L28 350 L4 (2S) (DENDRITIC CELL? OR MACROPHAGE? OR MONOCY? OR ANTIGEN
PRESENTING CELL? OR APC)

=> s l28 and (ex vivo or in vitro)
L29 75 L28 AND (EX VIVO OR IN VITRO)

=> dup rem l29
PROCESSING COMPLETED FOR L29
L30 33 DUP REM L29 (42 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 33 ANSWERS - CONTINUE? Y/(N):y

L30 ANSWER 1 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2002:210041 BIOSIS
DN PREV200200210041
TI CpG oligonucleotides: Novel regulators of osteoclast differentiation.
AU Zou, Wei; Schwartz, Harry; Endres, Stefan; Hartmann, Gunther; Bar-Shavit, Zvi (1)
CS (1) The H. Hubert Humphrey Center for Experimental Medicine and Cancer Research, The Hebrew University Faculty of Medicine, Jerusalem, 91120: barsha@cc.huji.ac.il Israel
SO FASEB Journal, (March, 2002) Vol. 16, No. 3, pp. 274-282. http://www.fasebj.org/. print.
ISSN: 0892-6638.
DT Article
LA English
AB The ***macrophage*** capability to recognize bacterial DNA is mimicked by oligodeoxynucleotides containing ***unmethylated*** CG dinucleotides ('CpG' motifs) in specific sequence contexts (CpG ODN). CpG ODN stimulates NF-kappaB activation in murine ***macrophages*** . In light of the pivotal role played by NF-kappaB in osteoclast differentiation, we examined the ability of CpG ODN to modulate osteoclastogenesis. CpG ODN alone induced TRAP-positive cells in bone marrow ***macrophage*** (BMM) cultures, but not multinucleation or calcitonin receptor expression. CpG ODN inhibited RANKL-induced osteoclastogenesis when present from the beginning of BMM culture, but strongly increased RANKL-induced osteoclastogenesis in RANKL-pretreated BMMs. CpG ODN enhanced the expression of interleukin 1beta (IL-1beta) and tumor necrosis factor alpha (TNF-alpha). Antibodies to TNF-alpha and the TNF type 1 receptor, but not the addition of IL-1 receptor antagonist, blocked CpG ODN-induced osteoclastogenesis in RANKL-pretreated cultures. On the other hand, CpG ODN reduced expression of the M-CSF receptor, which is critical during the initiation of osteoclast differentiation. These results suggest that CpG ODN, via the induction of TNF-alpha, support osteoclastogenesis in cells that are committed to the osteoclast differentiation pathway but, due to down-modulation of M-CSF receptor, inhibit early steps of osteoclast differentiation. Thus, CpG ODN represents a potential therapeutic tool for treating bone diseases.

L30 ANSWER 2 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
1
AN 2002:148790 BIOSIS
DN PREV200200148790
TI Monocytes are required for optimum in ***vitro*** stimulation of bovine peripheral blood mononuclear cells by non-methylated CpG motifs.
AU Pontarollo, R. A.; Rankin, R.; Babiuk, L. A.; Godson, D. L.; Griebel, P. J.; Hecker, R.; Krieg, A. M.; Littel-van den Hurk, S. van Drunen (1)
CS (1) Veterinary Infectious Disease Organization, University of Saskatchewan, 120 Veterinary Road, Saskatoon, SK, S7N 5E3: vandenhurk@sask.usask.ca Canada
SO Veterinary Immunology and Immunopathology, (1 January, 2002) Vol. 84, No. 1-2, pp. 43-59. print.
ISSN: 0165-2427.
DT Article
LA English
AB Bacterial DNA and synthetic oligodeoxynucleotides (ODN) containing ***unmethylated*** CpG motifs within certain flanking base pairs are recognized as a danger signal by the innate immune system of vertebrates. Using lymphocyte proliferative response (LPR) and IFN-gamma secretion assays, a panel of 38 ODN was screened for immunostimulatory activity on bovine peripheral blood mononuclear cells. ODN composed of a nuclease resistant phosphorothioate backbone and a leading 5'-TCGTCGTT-3' motif with two 5'-GTCGTT-3' motifs were highly stimulatory in both assays. Flow cytometric analysis and cell-specific surface marker labeling determined that B-cells (surface IgM+) were the primary cell population responding in the LPR assay. Depletion of T cells (CD3+) from the PBMC population did not affect IFN-gamma secretion or B-cell proliferation when cultured with CpG-ODN. However, depletion of ***monocytes*** (DH59B+) completely abrogated the ability of CpG-ODN to stimulate IFN-gamma secretion, and significantly reduced the B-cell proliferative response. These data establish the identity of an optimal immunostimulatory CpG motif for cattle and demonstrate that ***monocytes*** play a pivotal role in the ability of cell populations to respond to CpG-ODN. These data provide insight for future studies investigating the mechanism of CpG-ODN bioactivity and its application in novel vaccine formulations and immunotherapy.

L30 ANSWER 3 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2
AN 2001:187822 BIOSIS
DN PREV200100187822
TI Interleukin-12- and gamma interferon-dependent protection against malaria conferred by CpG oligodeoxynucleotide in mice.
AU Gramzinski, Robert A.; Doolan, Denise L.; Sedegah, Martha; Davis, Heather L.; Krieg, Arthur M.; Hoffman, Stephen L. (1)
CS (1) Malaria Program, Naval Medical Research Center, 503 Robert Grant Ave., Silver Spring, MD, 20910-7500: hoffmans@nmrc.navy.mil USA
SO Infection and Immunity, (March, 2001) Vol. 69, No. 3, pp. 1643-1649. print.
ISSN: 0019-9567.
DT Article
LA English
SL English
AB ***Unmethylated*** CpG dinucleotides in bacterial DNA or synthetic oligodeoxynucleotides (ODNs) cause B-cell proliferation and immunoglobulin secretion, ***monocyte*** cytokine secretion, and activation of natural killer (NK) cell lytic activity and gamma interferon (IFN-gamma) secretion in vivo and in ***vitro*** . The potent Th1-like immune activation by CpG ODNs suggests a possible utility for enhancing innate immunity against infectious pathogens. We therefore investigated whether the innate immune response could protect against malaria. Treatment of mice with CpG ODN 1826 (TCCATGACGTTCCTGACGTT, with the CpG dinucleotides underlined) or 1585 (ggGGTCAACGTTGAgggggG, with g representing diester linkages and phosphorothioate linkages being to the right of lowercase letters) in the absence of antigen 1 to 2 days prior to challenge with Plasmodium yoelii sporozoites conferred sterile protection against infection. A higher level of protection was consistently induced by CpG ODN 1826 compared with CpG ODN 1585. The protective effects of both CpG ODNs were dependent on interleukin-12, as well as IFN-gamma. Moreover, CD8+ T cells (but not CD4+ T cells), NK cells, and nitric oxide were implicated in the CpG ODN 1585-induced protection. These data establish that the protective mechanism induced by administration of CpG ODN 1585 in the absence of parasite antigen is similar in nature to the mechanism induced by immunization with radiation-attenuated P. yoelii sporozoites or with plasmid DNA encoding preerythrocytic-stage P. yoelii antigens. We were unable to confirm whether CD8+ T cells, NK cells, or nitric oxide were required for the CpG ODN 1826-induced protection, but this may reflect differences in the potency of the ODNs rather than a real difference in the mechanism of action of the two ODNs. This is the first report that stimulation of the innate immune system by CpG immunostimulatory motifs can confer sterile protection against malaria.

L30 ANSWER 4 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:258549 BIOSIS
DN PREV200100258549
TI CpG oligodeoxynucleotide (ODN) in combination with exogenous Ag, but not by itself alone, can break specific tolerance in transgenic mice.
AU Wang, Yiqiang (1); Krieg, Arthur M.
CS (1) University of Iowa, 540 EMRB, Iowa City, IA, IA52242 USA
SO FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1219. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB DNA containing ***unmethylated*** CpG dinucleotides in particular base contexts (CpG motifs) is a strong stimulator of innate and acquired immune responses. CpG ODN enhance ***dendritic*** ***cell*** and ***macrophage*** antigen presenting activity, and polyclonaly activate B cells. A tolerant model system including HEL-transgenic (Tg) mice, anti-HEL IgHa-Tg mice and double (Dbl)-Tg mice was used to study the effect of CpG ODN on tolerant B cells. B cells from Dbl-Tg mice expressed approximately 20 fold lower surface IgMa density compared with Ig-Tg B cells, consistent with the reported tolerant nature of these B cells. When cultured in ***vitro*** , these tolerant B cells are activated by CpG ODN in a similar pattern as Ig-Tg B cells, with RNA synthesis and proliferation that were synergistically increased by the combination of CpG ODN and specific Ag. Despite these in ***vitro*** responses, neither HEL-Tg mice nor Dbl-Tg mice produce any detectable anti-HEL Ab when injected with CpG ODN alone, or when immunized with CpG together with a moderate dose of antigen (40mug HEL), indicating a strong tolerant status in these mice. But mice immunized with CpG ODN together with a moderate or higher dose of antigen (40mug or 150mug HEL) gave strong antigen-specific humoral and cellular responses. In all experimental systems, control ODN without CpG motif gave no or much lower activity compared with CpG ODN. We conclude that immunization with CpG ODN in the presence of high dose endogenous antigen can break self tolerance, but that polyclonal stimulation by nonspecific agents alone is unlikely to do so.

L30 ANSWER 5 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
3
AN 2001:429083 BIOSIS
DN PREV200100429083
TI CpG DNA induces cyclooxygenase-2 expression and prostaglandin production.
AU Chen, Yongjin; Zhang, Juan; Moore, Steven A.; Ballas, Zuhair K.; Portanova, Joseph P.; Krieg, Arthur M.; Berg, Daniel J. (1)
CS (1) Department of Internal Medicine, University of Iowa College of Medicine, 200 Hawkins Drive, Iowa City, IA, 52242 USA
SO International Immunology, (August, 2001) Vol. 13, No. 8, pp. 1013-1020. print.
ISSN: 0953-8178.
DT Article
LA English
SL English
AB ***Unmethylated*** CpG motifs found in bacterial DNA are potent

activators of the innate and acquired immune systems, and rapidly induce the production of proinflammatory cytokines. We hypothesized that CpG DNA may also elicit the production of prostaglandins (PG), which are central lipid mediators of the immune and inflammatory response. To test our hypothesis, we stimulated murine spleen cells and RAW 264.7 murine ***macrophage*** cells with CpG DNA and assessed the effects on the PG synthesis pathway. Compared to control, DNA-containing CpG motifs induced >5-fold increase in PGE2 production and rapidly up-regulated cyclooxygenase-2 (COX-2) at both the mRNA and protein level. CpG DNA was an extremely strong inducer of COX-2 as concentrations as low as 3 ng/ml induced COX-2 protein expression. The CpG DNA-induced PGE2 down-regulated the immune response elicited by CpG. Blockade of PGE2 production with selective COX-2 inhibitors or neutralizing anti-PGE2 antibody markedly enhanced IFN-gamma secretion in ***vitro*** from CpG DNA-stimulated spleen cells. Moreover, selective COX-2 inhibition increased CpG DNA-induced IFN-gamma secretion in vivo. Inhibition of COX-2 also increased CpG DNA-induced lytic activity of NK cells. Taken together, these data indicate that DNA containing CpG motifs is a potent inducer of COX-2 and PGE2 production. CpG-induced PG may subsequently down-regulate the immune and inflammatory responses elicited by the CpG DNA.

L30 ANSWER 6 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
AN 2001:493428 BIOSIS
DN PREV200100493428
TI Immunostimulatory DNA from Paracoccidioides brasiliensis acts as T-helper 1 promoter in susceptible mice.
AU Souza, M. C.; Correa, M.; Almeida, S. R.; Lopes, J. D.; Camargo, Z. P. (1)
CS (1) Disciplina de Biologia Celular, Universidade Federal de Sao Paulo, Rua Botucatu, 862, 8 andar, 04023-062, Sao Paulo, S.P.: zoilo@ecb.epm.br Brazil
SO Scandinavian Journal of Immunology, (October, 2001) Vol. 54, No. 4, pp. 348-356. print.
ISSN: 0300-9475.
DT Article
LA English
SL English
AB Th1 immune responses afford protection against some pathogens like the fungus P. brasiliensis (P.b.), ethiological agent of Paracoccidioidomycosis (PCM). It is well known that nonmethylated CpG sequences from bacterial DNA have immunomodulatory properties and can be used as a Th1-promoting adjuvant. By analyzing the available gene sequences of P.b. we observed a high number of ***unmethylated*** CpG dinucleotides. In a murine model of the PCM infection, the isogenic mouse strain known to be susceptible presents a predominant Th2 pattern. In order to access the possibility of the genomic DNA to act as a Th1-promoting adjuvant, in ***vitro*** assays were made and indicated a significant increase in phagocytosis when the ***macrophages*** were stimulated with DNA from P.b. and in vivo assays of a decreased production of antibodies antigp43, the main antigen of the PCM system. The analysis of the antibody isotypes and the cytokine production suggested a Th1 modulation in the susceptible animals. Thus, when mice were infected with fungus plus synthetic oligodeoxynucleotide (ODN), made from the available sequence of gp43, a decrease in the fungus dissemination was observed. Results herein described suggest that genomic DNA from P.b. could have a immunostimulatory function as a Th-1 promoting adjuvant in susceptible mice.

L30 ANSWER 7 OF 33 MEDLINE DUPLICATE 5
AN 2001076819 MEDLINE
DN 20540079 PubMed ID: 11086059
TI APC stimulated by CpG oligodeoxynucleotide enhance activation of MHC class I-restricted T cells.
AU Warren T L; Bhatia S K; Acosta A M; Dahle C E; Ratliff T L; Krieg A M; Weiner G J
CS The Holden Cancer Center and Departments of Internal Medicine and Urology,
University of Iowa, Iowa City, IA 522421, USA.
NC RO1CA74542 (NCI)
T32 HL07344 (NHLBI)
SO JOURNAL OF IMMUNOLOGY, (2000 Dec 1) 165 (11) 6244-51.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200101
ED Entered STN: 20010322
Last Updated on STN: 20010910
Entered Medline: 20010111
AB Oligonucleotides containing ***unmethylated*** CpG motifs (cytosine-phosphorothioate-guanine oligodeoxynucleotide (CpG ODN)) are potent immunostimulatory agents capable of enhancing the Ag-specific Th1 response when used as immune adjuvants. We evaluated the cellular mechanisms responsible for this effect. Development of a CTL response was enhanced when mice were immunized with peptide-pulsed ***dendritic*** ***cells*** (DCs) treated with CpG ODN. However, in ***vitro*** , CpG ODN had no direct effect on highly purified T cells. In ***vitro*** , CpG ODN treatment of peptide- or protein-pulsed DCs enhanced the ability of the DCs to activate class I-restricted T cells. The presence of helper T cells enhanced this effect, indicating that treatment with CpG ODN does not obviate the role of T cell help. The enhanced ability of CpG ODN-treated DCs to activate T cells was present but blunted when DCs derived from IL-12 knockout mice were used. Fixation of Ag-pulsed, CpG ODN-treated DCs limited their ability to activate T cells. In contrast, fixation had little effect on DC activation of T cells when DCs were not exposed to CpG ODN. This indicates that production of soluble factors by DCs stimulated with CpG ODN plays a particularly important role in their ability to activate class I-restricted T cells. We conclude that CpG ODN enhances the development of a cellular immune response by stimulating APCs such as DCs, to produce IL-12 and other soluble factors.

L30 ANSWER 8 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:312490 BIOSIS
DN PREV200100312490
TI The treatment of 32D-BCR-ABL cells with 5-Aza-2'deoxycytidine prior to GM-CSF slows proliferation and induces differentiation.
AU Davies, C. S. (1); Walsh, V. A. (1); Al-Sabah, A. I. (1); Hoy, T. (1); Burnett, A. K. (1); Mills, K. I. (1)
CS (1) Haematology, University of Wales College of Medicine, Cardiff UK
SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 352a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DT Conference
LA English
SL English
AB Chronic myeloid leukaemia (CML) is associated with the accumulation of large numbers of immature myeloid cells. As the disease progresses, these myeloid cells fail to differentiate. No definitive cause for this abnormal differentiation pattern has yet been determined, however, it is possible that abnormal methylation may be contributory factors in this process. The in ***vitro*** effect of the demethylating agent 5-Aza-2'deoxycytidine (5AzaCdR) on the growth and differentiation of the murine myeloid cell line 32D and its BCR-ABL transformed counterparts, 32Db2a2 and 32Dp210 was investigated. Treatment with 5AzaCdR resulted in a decrease in cellular proliferation rate, which was most apparent in the BCR-ABL cell lines. This may be attributable to the activation of growth regulatory genes whose expression had been silenced by aberrant DNA methylation. This is supported, in the 32Dp210 cell line, by the induction in expression of the cell cycle regulatory gene p16INK4A following treatment with 5AzaCdR. Cell cycle analysis showed an increased proportion of cells in G0/1 following treatment with 5AzaCdR, which is consistent with the restoration of growth control. We examined whether demethylation, and possible induction of differentiation, mediated by 5AzaCdR rendered cells more responsive to the effects of GM-CSF. Treatment of 32Dp210 cells with 5AzaCdR prior to the differentiating agent GM-CSF restored growth control. This was accompanied by morphological and cell surface marker evidence of differentiation. An increased proportion of cells in G0/1 and a reciprocal decrease in cells in S phase was observed, consistent with the findings of differentiation induction. In summary, the pre-treatment of BCR-ABL transformed myeloid cells with 5AzaCdR leads to increased responsiveness to GM-CSF resulting in the loss of proliferative capacity and the generation of a more mature cell phenotype.

L30 ANSWER 9 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6
AN 2000:375951 BIOSIS
DN PREV200000375951
TI Modulation of interleukin-12 synthesis by DNA lacking the CpG motif and present in a mycobacterial cell wall complex.
AU Filion, Mario C. (1); Filion, Benoit; Reader, Stephanie; Menard, Sonia; Phillips, Nigel C.
CS (1) Bioniche Therapeutics Research Centre, Montreal, Quebec, H4P 2R2 Canada
SO Cancer Immunology Immunotherapy, (August, 2000) Vol. 49, No. 6, pp. 325-334. print.
ISSN: 0340-7004.
DT Article
LA English
SL English
AB A mycobacterial cell wall complex prepared from the non-pathogenic microorganism Mycobacterium phlei, where mycobacterial DNA is preserved and complexed to cell wall fragments, possesses anticancer and immunomodulatory activity. DNA from a number of prokaryotes has been found to modulate the immune system and to induce cytokine synthesis. We have therefore determined whether the DNA associated with this complex has the ability to induce the synthesis of interleukin-12 (IL-12), a potent anticancer cytokine. Mycobacterial DNA complexed with cell wall fragments or DNA purified from M. phlei induced IL-12 synthesis by murine and human ***monocytes*** and ***macrophages*** in ***vitro*** , and was capable of inducing IL-12 synthesis in vivo in mice following i.p. administration. Neutralization of DNA with cationic liposomes or digestion with DNase I significantly decreased the ability of the cell wall complex to induce IL-12. CpG methylation of DNA extracted from these cell walls or from M. phlei did not affect the induction of IL-12 synthesis by ***monocytes*** and ***macrophages*** . In contrast, CpG methylation of DNA from Escherichia coli abolished its ability to induce IL-12 synthesis. These results demonstrate that ***unmethylated*** CpG

motifs present in M. phlei DNA are not a prerequisite for the induction of IL-12 synthesis. The size of the mycobacterial DNA, in the range of 5 bp to genomic DNA, did not influence its capacity to induce IL-12. Our results emphasize that M. phlei DNA associated with the cell wall complex makes a significant contribution to the overall immunomodulatory and anticancer activity of this mycobacterial cell wall preparation and that these activities are not correlated with the presence of CpG motifs.

L30 ANSWER 10 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 7
AN 2001:141766 BIOSIS
DN PREV200100141766
TI CpG oligodeoxynucleotides induce murine macrophages to up-regulate chemokine mRNA expression.
AU Takeshita, Saoko (1); Takeshita, Fumihiko (1); Haddad, Diana E.; Ishii, Ken J. (1); Klinman, Dennis M. (1)
CS (1) Section of Retroviral Immunology, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD, 20892 USA
SO Cellular Immunology, (December 15, 2000) Vol. 206, No. 2, pp. 101-106. print.
ISSN: 0008-8749.
DT Article
LA English
SL English
AB Intramuscular injection of synthetic oligodeoxynucleotides (ODN) expressing ***unmethylated*** CpG motifs trigger the rapid development of a local inflammatory response. In ***vitro*** studies demonstrate that ***macrophages*** exposed to CpG ODN up-regulate expression of mRNA encoding the chemokines MIP-1alpha, MIP-1beta, MIP-2, RANTES, JE/MCP-1, and IP-10. Within 6 h of in vivo administration, CpG ODN induce a significant increase in chemokine mRNA levels at the site of injection and draining lymph nodes. These chemokines may contribute to the migration and stimulation of inflammatory cells that contribute to the development of CpG ODN-induced immune responses.

L30 ANSWER 11 OF 33 MEDLINE DUPLICATE 8
AN 2001084160 MEDLINE
DN 20401099 PubMed ID: 10944802
TI Multiple effects of immunostimulatory DNA on T cells and the role of type I interferons.
AU Sun S; Zhang X; Tough D; Sprent J
CS R.W. Johnson Pharmaceutical Research Institute, La Jolla, CA 92121, USA.
NC AI32068 (NIAID)
CA25803 (NCI)
CA38355 (NCI)
+
SO SPRINGER SEMINARS IN IMMUNOPATHOLOGY, (2000) 22 (1-2) 77-84. Ref: 26
Journal code: VBG. ISSN: 0172-6641.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200101
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010118
AB In addition to stimulating antigen-specific immune responses, infectious agents cause nonspecific activation of the innate immune system, notably up-regulation of costimulatory/adhesion molecules on APCs and cytokine production. In recent years it has become apparent that stimulation of the immune system by microorganisms is a property of a number of different cellular components, including DNA. As discussed earlier and elsewhere in this volume, the DNA of infectious agents--and indeed of all non-vertebrates tested--differs from mammalian DNA in being enriched for ***unmethylated*** CpG motifs. With appropriate flanking sequences, CpG DNA and synthetic CpG ODNs cause strong activation of APCs and other cells. In this article we have focussed on the capacity of CpG DNA/ODNs to alter T cell function. Whether these compounds act directly on T cells or function indirectly by activating other cells, especially APCs, is controversial [7, 8, 13, 14]. In contrast to other workers [8], we have yet to find definitive evidence that CpG DNA/ODNs can provide a co-stimulatory signal for purified T cells subjected to TCR ligation ([14] and unpublished data of authors). For this reason we lean to the notion that CpG DNA/ODNs modulate T cell function by inducing activation of ***APC*** rather than by acting directly on T cells. When injected in vivo in the absence of specific antigen, CpG DNA/ODNs have two striking effects on T cells, namely (1) induction of overt activation (proliferation) of memory-phenotype CD8+ cells, and (2) partial activation of all T cells, including naive-phenotype T cells. Both actions of CpG DNA/ODNs are heavily dependent on the production of IFN-I by ***APC*** . For memory-phenotype (CD44hi) CD8+ cells, neither CpG DNA nor IFN-I can cause proliferation of purified ***APC*** -depleted T cells in ***vitro*** . Hence, under in vivo conditions, CpG DNA-induced proliferation of CD44hi CD8+ cells is probably mediated through the production of a secondary cytokine, i.e., by a cytokine that is directly stimulatory for CD44hi CD8+ cells. Based on the available evidence, it is highly likely that the effector cytokine is IL-15. With this assumption, our current model is that proliferation of CD44hi CD8+ cells induced by injection of CpG DNA/ODNs reflects production of IFN-I which, in turn, leads to synthesis of IL-15. Which particular cell types produce these two cytokines is unclear, although APCs are probably of prime importance. In addition to inducing proliferation of memory-phenotype CD8+ cells via IL-15, the IFN-I induced by CpG DNA/ODNs can also induce partial activation of naive T cells. This form of activation leads to up-regulation of CD69 and other molecules but does not cause entry into cell cycle. It is of interest that the partial activation of naive T cells induced by IFN-I is associated with decreased T proliferative responses. Thus, proliferation of purified naive T cells elicited by combined TCR/CD28 ligation in ***vitro*** is greatly reduced by addition of IFN-I. This inhibitory effect of IFN-I does not influence cytokine production and probably reflects production of cell cycle inhibitors. Surprisingly, except at high doses, IFN-I fails to exert an anti-proliferative effect when T proliferative responses are driven by viable APCs. Indeed, in this situation, IFN-I enhances antigen-specific T proliferative responses, both in vivo and in ***vitro*** . This adjuvant effect of IFN-I is presumably a reflection of ***APC*** activation, but direct evidence on this issue is still lacking. In this article we have emphasized that contact with CpG DNA/ODNs has multiple effects on T cell function in vivo. Many of these effects seem to be related to the production of certain cytokines by APCs, notably IFN-I and IL-15. It should be stressed, however, that CpG DNA/ODNs probably lead to the production of many other cytokines. Hence, our current models of how CpG DNA/ODNs influence T cell function are undoubtedly oversimplified.

L30 ANSWER 12 OF 33 MEDLINE DUPLICATE 9
AN 2000040386 MEDLINE
DN 20040386 PubMed ID: 10570281
TI Phosphorothioate oligodeoxynucleotides promote the in ***vitro*** development of human allergen-specific CD4+ T cells into Th1 effectors.
AU Parronchi P; Brugnolo F; Annunziato F; Manuelli C; Sampognaro S; Mavilia C; Romagnani S; Maggi E
CS Department of Internal Medicine, Immunoallergology and Respiratory Disease Unit, University of Florence, Florence, Italy.
SO JOURNAL OF IMMUNOLOGY, (1999 Dec 1) 163 (11) 5946-53.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199912
ED Entered STN: 20000113
Last Updated on STN: 20000113
Entered Medline: 19991220
AB DNA vaccination is an effective approach in inducing the switch of murine immune responses from a Th2 to a Th1 profile of cytokine production that has been related to the activity of ***unmethylated*** CpG motifs present in bacterial, but not mammalian, DNA. We report here that some synthetic phosphorothioate, but not phosphodiester, oligodeoxynucleotides (ODNs) were able to induce B cell proliferation and to shift the in ***vitro*** differentiation of Dermatophagoides pteronyssinus group 1-specific human CD4+ T cells from atopic donors into Th cell effectors showing a prevalent Th1, instead of Th2, cytokine profile. This latter effect was completely blocked by the neutralization of IL-12 and IFN (alpha and gamma) in bulk culture, suggesting that the Th1-inducing activity of phosphorothioate ODNs was mediated by their ability to stimulate the production of these cytokines by ***monocytes*** , dendritic, and NK cells. Cytosine methylation abolished the Th1-inducing activity of ODNs; however, CpG dinucleotide-containing ODNs exhibited the Th1-shifting effect independently of the presence or the absence of CpG motifs (5'-pur-pur-CpG-pyr-pyr-3'). Moreover, the inversion of CpG to GpC resulted only in a partial reduction of this activity, suggesting that the motif responsible for the Th1-skewing effect in humans is at least partially different from that previously defined in mice. These results support the concept that the injection of allergens mixed to, or conjugated with, appropriate ODNs may provide a novel allergen-specific immunotherapeutic regimen for the treatment of allergic disorders.

L30 ANSWER 13 OF 33 MEDLINE DUPLICATE 10
AN 1999421811 MEDLINE
DN 99421811 PubMed ID: 10490958
TI Oligodeoxynucleotides containing palindrome sequences with internal 5'-CpG-3' act directly on human NK and activated T cells to induce IFN-gamma production in ***vitro*** .
AU Iho S; Yamamoto T; Takahashi T; Yamamoto S
CS Department of Immunology, Faculty of Medicine, Fukui Medical University, Japan.. ihosumik@fmsrsa.fukui-med.ac.jp
SO JOURNAL OF IMMUNOLOGY, (1999 Oct 1) 163 (7) 3642-52.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199910
ED Entered STN: 19991101
Last Updated on STN: 19991101
Entered Medline: 19991021
AB Previous studies have shown that the action of bacterial or synthetic oligodeoxynucleotide (oligo-DNA) on mouse NK cells to produce IFN-gamma is mediated mostly by ***monocytes*** / ***macrophages*** activated by olig-DNA. However, its action on human IFN-gamma-producing cells has not been well investigated. In the present study, we examined the effect of oligo-DNAs on highly purified human NK and T cells. Bacillus

Calmette-Guerin-derived or synthetic oligo-DNAs induced NK cells to produce IFN-gamma with an increased CD69 expression, and the autocrine IFN-gamma enhanced their cytotoxicity. The response of NK cells to oligo-DNAs was enhanced when the cells were activated with IL-2, IL-12, or anti-CD16 Ab. T cells did not produce IFN-gamma in response to oligo-DNAs but did respond independently of IL-2 when they were stimulated with anti-CD3 Ab. In the action of oligo-DNAs, the palindrome sequence containing ***unmethylated*** 5'-CpG-3' motif(s) appeared to play an important role in the IFN-gamma-producing ability of NK cells. The changes of base composition inside or outside the palindrome sequence altered its activity: The homooligo-G-flanked GACGATCGTC was the most potent IFN-gamma
inducer for NK cells. The CG palindrome was also important for activated NK and T cells in their IFN-gamma production, although certain nonpalindromes acted on them. Among the sequences tested, cell activation- or cell lineage-specific sequences were likely; i.e., palindrome ACCGGT and nonpalindrome AACGAT were favored by activated NK cells but not by unactivated NK cells or activated T cells. These results indicate that oligo-DNAs containing CG palindrome act directly on human NK cells and activated T cells to induce IFN-gamma production.

L30 ANSWER 14 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
11
AN 1999:523214 BIOSIS
DN PREV199900523214
TI Cytosine demethylation of the proteinase-3/myeloblastin primary granule protease gene during phagocyte development.
AU Luebbert, M. (1); Tobler, A.; Daskalakis, M.
CS (1) Department of Hematology/Oncology, University of Freiburg Medical Center, Hugstetter Str 55, D-79106, Freiburg Germany
SO Leukemia (Basingstoke), (Sept., 1999) Vol. 13, No. 9, pp. 1420-1427.
ISSN: 0887-6924.
DT Article
LA English
SL English
AB Proteinase-3/Myeloblastin (Mbn) is a neutral serine protease and a major constituent of the primary granules of myeloid cells. It can degrade extracellular matrix proteins and has been discussed as a key factor for the initiation of terminal differentiation in promyelocytic cells.
Regulation of Mbn closely parallels that of another major primary granule protein, myeloperoxidase (MPO). We examined the expression and DNA methylation of Mbn in a model of in ***vitro*** differentiation of CD34+ enriched peripheral blood progenitor cells (PBPCs), and in various other myeloid and non-myeloid tissues. Mbn mRNA was undetectable in uncultured PBPCs but was upregulated during their in ***vitro*** differentiation. Its expression was enhanced in the presence of G-CSF. Mbn expression was also detected in several myeloid cell lines but not in mature granulocytes, ***monocytes*** and ***macrophages*** . Partial ***demethylation*** at a CpG site within Mbn intron 1 (analyzed by restriction with SmaI) was observed during continued in ***vitro*** differentiation of PBPCs. This site was fully ***demethylated*** in mature granulocytes, ***monocytes*** and ***macrophages*** . Variable methylation of this site and a second SmaI site located upstream of the putative Mbn promoter region was present in other myeloid and non-myeloid tissues examined.

L30 ANSWER 15 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
12
AN 1999:300763 BIOSIS
DN PREV199900300763
TI Bacterial DNA and CpG-containing oligodeoxynucleotides activate cutaneous dendritic cells and induce IL-12 production: Implications for the augmentation of Th1 responses.
AU Jakob, Thilo (1); Walker, Patricia S.; Krieg, Arthur M.; von Stebut, Esther; Udey, Mark C.; Vogel, Jonathan C.
CS (1) Klinik und Poliklinik fuer Dermatologie und Allergologie, Technische Universitaet Muenchen, Biedersteiner Strasse 29, D-80802, Muenchen Germany
SO International Archives of Allergy and Immunology, (Feb.-April, 1999) Vol. 118, No. 2-4, pp. 457-461.
ISSN: 1018-2438.
DT Article
LA English
SL English
AB Background: ***Unmethylated*** CpG sequences in bacterial DNA act as adjuvants selectively inducing Th1 predominant immune responses during genetic vaccination or when used in conjunction with protein Ag. The precise mechanism of this adjuvant effect is unknown. Because ***dendritic*** ***cells*** (DC) are thought to be crucially involved in T cell priming and Th1/Th2 education during vaccination via skin, we characterized the effects of bacterial DNA and CpG-containing oligodeoxynucleotides (CpG ODN) on cutaneous DC. Methods and Results: Stimulation with CpG ODN 1826 (6 mug/ml) induced activation of immature Langerhans cell (LC)-like DC as determined by an increased expression of MHC class II and costimulatory molecules, loss of E-cadherin-mediated adhesion and increased ability to stimulate allogeneic T cells. Composition-matched control ODN 1911 lacking CpG sequences at equal concentrations was without effect. In comparison to LPS and ODN 1911, CpG ODN 1826 selectively stimulated DC to release largeamounts of IL-12 (p40) and little IL-6 or TNF-alpha within 18 h and detectable levels of IL-12 p70 within 72 h. Stimulation with Escherichia coli DNA, but not calf thymus DNA, similarly induced DC maturation and IL-12 p40 production. Injection of CpG ODN into murine dermis induced enhanced expression of MHC class II and CD86 by LC in the overlying epidermis and intracytoplasmic IL-12 p40 accumulation in a subpopulation of activated LC. Conclusion: Bacterial DNA and CpG ODN stimulate DC in ***vitro*** and in vivo and may preferentially elicit Th1-predominant immune responses because they can activate and mobilize DC, inducing them to produce IL-12.

L30 ANSWER 16 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
13
AN 1999:299879 BIOSIS
DN PREV199900299879
TI DNA global hypomethylation in EBV-transformed interphase nuclei.
AU Habib, M.; Fares, F.; Bourgeois, C. A.; Bella, C.; Bernardino, J.; Hernandez-Blazquez, F.; de Capoa, A.; Niveleau, A. (1)
CS (1) Laboratoire de Virologie, Faculte de Medecine, UPRES-A CNRS 5082, Universite Joseph Fourier de Grenoble, Domaine de La Merci, 38706, La Tronche Cedex France
SO Experimental Cell Research, (May 25, 1999) Vol. 249, No. 1, pp. 46-53.
ISSN: 0014-4827.
DT Article
LA English
SL English
AB In tumors, DNA is often globally ***hypomethylated*** compared to DNA extracted from normal tissues. This observation is usually made after extraction and exhaustive digestion of DNA followed by analysis of nucleosides by chromatography or digestion with restriction enzymes, gel analysis, and hybridization. This approach provides an average value which does not give information on the various cell subpopulations included in heterogeneous samples. Therefore an immunochemical technique was set up with the aim of demonstrating, in a population of mixed cells, the possibility of detecting the presence of individual nuclei containing ***hypomethylated*** DNA, on a cell-by-cell basis. Monoclonal antibodies to 5-methylcytidine were used to label cells grown in ***vitro*** . Under appropriate fixation and permeabilization conditions, interphase nuclei were labeled. Quantitative differences in the labeling were detected between Epstein-Barr virus-transformed cells and normal peripheral blood ***monocytes*** by flow cytometry analysis. Similar differences were observed by fluorescence microscopy. Both results were confirmed by Southern transfer and hybridization of DNA fragments generated by restriction enzyme digestion. This observation, which is in accordance with the occurrence of global DNA ***hypomethylation*** in tumors as established by chromatography, opens the field for the analysis of fresh tumor samples by flow cytometry and microscopy.

L30 ANSWER 17 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
14
AN 1998:496885 BIOSIS
DN PREV199800496885
TI Sequence motifs in adenoviral DNA block immune activation by stimulatory CpG motifs.
AU Krieg, Arthur M. (1); Wu, Tong; Weeratna, Risini; Efler, Susan M.; Love-Homan, Laurie; Yang, Lin; Yi, Ae-Kyung; Short, Dan; Davis, Heather L.
CS (1) Univ. Iowa, Dep. Intern. Med., 540 EMRB, Iowa City, IA 52242 USA
SO Proceedings of the National Academy of Sciences of the United States of America, (Oct. 13, 1998) Vol. 95, No. 21, pp. 12631-12636.
ISSN: 0027-8424.
DT Article
LA English
AB ***Unmethylated*** CpG dinucleotides in particular base contexts (CpG-S motifs) are relatively common in bacterial DNA but are rare in vertebrate DNA. B cells and ***monocytes*** have the ability to detect such CpG-S motifs that trigger innate immune defenses with production of Th1-like cytokines. Despite comparable levels of ***unmethylated*** CpG dinucleotides, DNA from serotype 12 adenovirus is immune-stimulatory, but serotype 2 is nonstimulatory and can even inhibit activation by bacterial DNA. In type 12 genomes, the distribution of CpG-f flanking bases is similar to that predicted by chance. However, in type 2 adenoviral DNA the immune stimulatory CpG-S motifs are outnumbered by a 15- to 30-fold excess of CpG dinucleotides in clusters of direct repeats or with a C on the 5' side or a G on the 3' side. Synthetic oligodeoxynucleotides containing these putative neutralizing (CpG-N) motifs block immune activation by CpG-S motifs in ***vitro*** and in vivo. Eliminating 52 of the 134 CpG-N motifs present in a DNA vaccine markedly enhanced its Th1-like function in vivo, which was increased further by the addition of CpG-S motifs. Thus, depending on the CpG motif, prokaryotic DNA can be either immune-stimulatory or neutralizing. These results have important implications for understanding microbial pathogenesis and molecular evolution and for the clinical development of DNA vaccines and gene therapy vectors.

L30 ANSWER 18 OF 33 MEDLINE DUPLICATE 15
AN 1998414301 MEDLINE
DN 98414301 PubMed ID: 9743369
TI Activation of cutaneous dendritic cells by CpG-containing oligodeoxynucleotides: a role for dendritic cells in the augmentation of Th1 responses by immunostimulatory DNA.
AU Jakob T; Walker P S; Krieg A M; Udey M C; Vogel J C
CS Dermatology Branch, National Cancer Institute, Bethesda, MD 20892-1908, USA.
SO JOURNAL OF IMMUNOLOGY, (1998 Sep 15) 161 (6) 3042-9.

Journal code: IFB; 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199810
ED Entered STN: 19981020
Last Updated on STN: 19981020
Entered Medline: 19981006
AB Genetic vaccination depends at least in part on the adjuvant properties of plasmids, properties that have been ascribed to ***unmethylated*** CpG dinucleotides in bacterial DNA. Because ***dendritic*** ***cells*** (DC) participate in the T cell priming that occurs during genetic vaccination, we reasoned that CpG-containing DNA might activate DC. Thus, we assessed the effects of CpG oligodeoxynucleotides (CpG ODN) on Langerhans cell (LC)-like murine fetal skin-derived DC (FSDDC) in ***vitro*** and on LC in vivo. Treatment with CpG ODN as well as LPS induced FSDDC maturation, manifested by decreased E-cadherin-mediated adhesion, up-regulation of MHC class II and costimulator molecule expression, and acquisition of enhanced accessory cell activity. In contrast to LPS, CpG ODN stimulated FSDDC to produce large amounts of IL-12 but only small amounts of IL-6 and TNF-alpha. Injection of CpG ODN into murine dermis also led to enhanced expression of MHC class II and CD86 Ag by LC in overlying epidermis and intracytoplasmic IL-12 accumulation in a subpopulation of activated LC. We conclude that immunostimulatory CpG ODN stimulate DC in ***vitro*** and in vivo. Bacterial DNA-based vaccines may preferentially elicit Th1-predominant immune responses because they activate and mobilize DC and induce them to produce large amounts of IL-12.

L30 ANSWER 19 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
16
AN 1999:87690 BIOSIS
DN PREV199900087690
TI Type I interferon-mediated stimulation of T cells by CpG DNA.
AU Sun, Siquan; Zhang, Xiaohong; Tough, David F.; Sprent, Jonathan (1)
CS (1) Dep. Immunol., IMM4, Scripps Res. Inst., 10550 N. Torrey Pines Rd., La Jolla, CA 92037 USA
SO Journal of Experimental Medicine, (Dec. 21, 1998) Vol. 188, No. 12, pp. 2335-2342.
ISSN: 0022-1007.
DT Article
LA English
AB Immunostimulatory DNA and oligodeoxynucleotides containing ***unmethylated*** CpG motifs (CpG DNA) are strongly stimulatory for B cells and ***antigen*** - ***presenting*** ***cells*** (APCs). We report here that, as manifested by CD69 and B7-2 upregulation, CpG DNA also induces partial activation of T cells, including naive-phenotype T cells, both in vivo and in ***vitro*** . Under in ***vitro*** conditions, CpG DNA caused activation of T cells in spleen cell suspensions but failed to stimulate highly purified T cells unless these cells were supplemented with APCs. Three lines of evidence suggested that ***APC*** -dependent stimulation of T cells by CpG DNA was mediated by type I interferons (IFN-I). First, T cell activation by CpG DNA was undetectable in IFNIR-/- mice. Second, in contrast to normal T cells, the failure of purified IFN-IR-/- T cells to respond to CpG DNA could not be overcome by adding normal IFN-IR+ APCs. Third, IFN-I (but not IFN-gamma) caused the same pattern of partial T cell activation as CpG DNA. Significantly, T cell activation by IFN-I was ***APC*** independent. Thus, CpG DNA appeared to stimulate T cells by inducing APCs to synthesize IFN-1, which then acted directly on T cells via IFN-IR. Functional studies suggested that activation of T cells by IFN-I was inhibitory. Thus, exposing normal (but not IFN-IR-/-) T cells to CpG DNA in vivo led to reduced T proliferative responses after TCR ligation in ***vitro*** .

L30 ANSWER 20 OF 33 MEDLINE DUPLICATE 17
AN 1998211649 MEDLINE
DN 98211649 PubMed ID: 9551923
TI CpG DNA is a potent enhancer of specific immunity in mice immunized with recombinant hepatitis B surface antigen.
CM Erratum in: J Immunol 1999 Mar 1;162(5):3103
Erratum in: Weeranta R[corrected to Weeratna R]
AU Davis H L; Weeratna R; Waldschmidt T J; Tygrett L; Schorr J; Krieg A M; Weeranta R
CS Loeb Research Institute, Ottawa Civic Hospital, ON, Canada..
hdavis@civich.ottawa.on.ca
NC DK25295 (NIDDK)
R29AR42556 (NIAMS)
RO1 AI31265 (NIAID)
+
SO JOURNAL OF IMMUNOLOGY, (1998 Jan 15) 160 (2) 870-6.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199804
ED Entered STN: 19980507
Last Updated on STN: 20000303
Entered Medline: 19980430
AB ***Unmethylated*** CpG dinucleotides in bacterial DNA or synthetic oligodeoxynucleotides (ODN) cause B cell proliferation and Ig secretion, ***monocyte*** cytokine secretion, and activation of NK cell lytic activity and IFN-gamma secretion in vivo and in ***vitro*** . The potent immune activation by CpG ODN suggests possible utility for enhancing immune responses to vaccines. Mice immunized with recombinant hepatitis B virus surface Ag and a CpG ODN as an immune enhancer have titers of Abs against HBsAg (anti-HBs) that are five times higher than those of mice immunized with HBsAg and the standard adjuvant, aluminum hydroxide (alum). Ab titers in mice immunized with HBsAg and both CpG ODN plus alum were 35 times higher than the titers in mice immunized with alum alone, indicating a strong synergistic interaction between the CpG ODN and alum. ODN without CpG motifs had little or no immune-enhancing activity at the doses used herein. Alum induces a Th2 humoral response (mostly IgG1) and no CTL. In contrast, CpG ODN gives a strong Th1 response with predominantly IgG2a Abs and CTL, even when mixed with alum. In ***vitro*** studies to determine possible mechanisms of CpG immune-enhancing effects show that CpG ODN induce expression of costimulatory molecules on Ag-presenting cells and drive B cell isotype switching in the appropriate cytokine milieu. These studies demonstrate that CpG ODN are promising new immune enhancers for vaccination applications.

L30 ANSWER 21 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
18
AN 1998:78403 BIOSIS
DN PREV199800078403
TI Immunostimulatory DNA: Sequence-dependent production of potentially harmful or useful cytokines.
AU Lipford, Grayson B.; Sparwasser, Tim; Bauer, Marc; Zimmermann, Stefan; Koch, Eva-Sophie; Heeg, Klaus; Wagner, Hermann (1)
CS (1) Inst. Med. Microbiol. Immunol. Hyg., Trogerstr. 9, D-81675 Munich Germany
SO European Journal of Immunology, (Dec., 1997) Vol. 27, No. 12, pp. 3420-3426.
ISSN: 0014-2980.
DT Article
LA English
AB Certain bacterial immunostimulatory (i.s.) DNA sequences containing ***unmethylated*** CpG motifs stimulate ***antigen*** - ***presenting*** ***cells*** (***APC***) to express a full complement of costimulatory molecules and to produce cytokines including interleukin (IL)-12 and tumor necrosis factor (TNF)-alpha. While IL-12 is key to their T helper cell (Th)1 -promoting adjuvant activity, secretion of toxic levels of TNF-alpha is harmful in that it promotes toxic shock. Given the beneficial as well as harmful consequences of i.s. DNA, we investigated the possibility of identifying DNA sequences, i.e. CpG oligodeoxynucleotides (ODN) which differentially activate IL-12 versus TNF-alpha cytokine production in ***APC*** . Here, we describe an i.s. DNA sequence with these characteristics. While its potential to induce IL-12 is preserved, its ability to trigger TNF-alpha release is strongly curtailed both in ***vitro*** and in vivo. I.s. DNA could be segregated into lethal and non-lethal in a mouse toxic shock model. The non-toxic i.s. DNA was useful as an adjuvant, thus allowing cytotoxic T cell responses to the soluble protein ovalbumin and conferring a resistant Th 1 phenotype to BALB/c mice lethally infected with Leishmania major. This i.s. CpG motif may thus be prototypic for a useful immunostimulating DNA sequence that lacks harmful side effects.

L30 ANSWER 22 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
19
AN 1997:367353 BIOSIS
DN PREV199799659286
TI Macrophages sense pathogens via DNA motifs: Induction of tumor necrosis factor-alpha-mediated shock.
AU Sparwasser, Tim; Miethke, Thomas; Lipford, Grayson; Erdmann, Andreas; Haecker, Hans; Heeg, Klaus; Wagner, Hermann (1)
CS (1) Inst. Med. Mikrobiologie, Immunology an Hygiene der TUM, Trogerstr. 9, D-81675 Muenchen Germany
SO European Journal of Immunology, (1997) Vol. 27, No. 7, pp. 1671-1679.
ISSN: 0014-2980.
DT Article
LA English
AB Cell surface components of pathogens, such as lipopolysaccharide (LPS), are an important signal for receptor-mediated activation of immune cells. Here we demonstrate that DNA of gram-positive and gram-negative bacteria or certain synthetic oligonucleotides displaying ***unmethylated*** CpG-motifs can trigger ***macrophages*** in ***vitro*** to induce nuclear translocation of nuclear factor-kappa-B, accumulate tumor necrosis factor (TNF)-alpha mRNA and release large amounts of TNF-alpha. In vivo these events culminate in acute cytokine-release syndrome which includes systemic but transient accumulation of TNF-alpha. D-Galactosamine (D-GalN)-sensitized mice succumb to lethal toxic shock due to ***macrophage*** -derived TNF-alpha resulting in fulminant apoptosis of liver cells. LPS and a specific oligonucleotide synergized in vivo as measured by TNF-alpha-release, suggesting that ***macrophages*** integrate the respective signals. The ability of ***macrophages*** to discriminate and to respond to bacterial DNA with acute release of proinflammatory cytokines may point out an important and as yet unappreciated sensing mechanism for foreign DNA.

L30 ANSWER 23 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE

20
AN 1997:18940 BIOSIS
DN PREV199799318143
TI In vivo protein interaction with the mouse M-lysozyme gene downstream enhancer correlates with demethylation and gene expression.
AU Short, Marc L.; Nickel, Joachim; Schmitz, Alexander; Renkawitz, Rainer (1)
CS (1) Inst. Genet., Justus Liebig Univ., Heinrich-Buff-Ring 58-62, 35392 Giessen Germany
SO Cell Growth & Differentiation, (1996) Vol. 7, No. 11, pp. 1545-1550. ISSN: 1044-9523.
DT Article
LA English
AB Differentiation of myeloid precursor cells results in transcriptional activation of the myeloid-specific murine M-lysozyme gene. M-lysozyme gene expression depends on the differentiation state of the myeloid cells and provides a marker for myeloid leukemias. The mouse lysozyme downstream enhancer (MLDE) was colocalized previously with the DNase I hypersensitive site in the chromatin of mature ***macrophages*** and shown to be ***macrophage*** differentiation-dependent. The correlation of the hypersensitive site appearance with expression of the M-lysozyme gene suggests that the enhancer becomes activated during ***macrophage*** differentiation. However, the predominant MLDE-binding protein GABP is ubiquitously expressed, indicating that additional regulatory mechanisms are required for restricting the tissue-specific activity of the enhancer. To demonstrate the specificity of the enhancer in vivo, we examined the in vivo interaction of factors with the MLDE in T cells, immature ***macrophage*** cells, and in ***macrophage*** cells. Although identical DNase I protection activity is present in extracts from all tested cell lines in ***vitro*** , the in vivo interaction of proteins is restricted to mature ***macrophage*** cells. The presence of factors capable of interacting with the enhancer is not sufficient for enhancer activity, suggesting that the process of differentiation results in factor accessibility for the MLDE. Analysis of the MLDE methylation state revealed a correlation between ***demethylation*** of the single CpG dinucleotide within the MLDE sequence and the in vivo interaction of proteins.

L30 ANSWER 24 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
21
AN 1996:55545 BIOSIS
DN PREV199698627680
TI Methylation of the mouse M-lysozyme downstream enhancer inhibits heterotetrameric GABP binding.
AU Nickel, Joachim; Short, Marc L.; Schmitz, Alexander; Eggetrt, Martin; Renkawitz, Rainer (1)
CS (1) Genetisches Inst. Justus-Liebig Univ., Heinrich-Buff-Ring 58-62, 35392 Giessen Germany
SO Nucleic Acids Research, (1995) Vol. 23, No. 23, pp. 4785-4792. ISSN: 0305-1048.
DT Article
LA English
AB Expression of the mouse M-lysozyme gene is a specific marker for the differentiation of ***macrophage*** /granulocyte cell lineages. Analysis of the mechanisms regulating M-lysozyme gene expression revealed an enhancer element in the 3'-flanking region of the gene, termed the M-lysozyme downstream enhancer (MLDE). Here we demonstrate that the nuclear factors binding to MLDE are present in all tested myeloid and non-myeloid mouse cell lines. Sequence analysis of MLDE identified two different sequences, CAGGAAGT and CCGGAAGT, which match the consensus binding sequences for proteins of the ets gene superfamily. The two sites are oriented palindromicly and separated by 10 bp. DMS/DEPC interference assays revealed different patterns of DNA-protein contacts on the two sites. Mutation of each consensus sequence leads to an individual change in protein binding in ***vitro*** . Despite these differences, both sequences are bound by GABP, forming a heterotetrameric complex. Tissue specificity is correlated with ***demethylation*** of a single CpG dinucleotide located in one of the two Ets motifs. This site when methylated inhibits GABP binding to both sequences in non-***macrophage*** cell types.

L30 ANSWER 25 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
22
AN 1993:138143 BIOSIS
DN PREV199395070943
TI Synergism in ***vitro*** of lovastatin and miconazole as anti-leishmanial agents.
AU Haughan, Penny A.; Chance, Michael L.; Goad, L. John (1)
CS (1) Dep. Biochem., Univ. Liverpool, P.O. Box 147, Liverpool L69 3BX UK
SO Biochemical Pharmacology, (1992) Vol. 44, No. 11, pp. 2199-2206. ISSN: 0006-2952.
DT Article
LA English
AB The antifungal drug miconazole and the cholesterol-lowering agent lovastatin (mevinolin) were used in combination to assess their potency as anti-leishmanial agents. The drug combination was synergistic, being more potent in terms of inhibitor of promastigote proliferation, ***macrophage*** infection and amastigote numbers. In promastigote culture the effect was more marked in Leishmania amazonensis than L. donovani. Analysis of the sterol compositions of both promastigote and amastigote cultures revealed the inhibition of sterol 14-alpha-***demethylation*** by miconazole and showed some apparent evidence of inhibition of sterol biosynthesis by lovastatin.

L30 ANSWER 26 OF 33 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 90011305 EMBASE
DN 1990011305
TI The immunopathogenesis of HIV infection.
AU Rosenberg Z.F.; Fauci A.S.
CS National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, United States
SO Advances in Immunology, (1989) 47/- (377-431). ISSN: 0065-2276 CODEN: ADIMAV
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
047 Virology
LA English
SL English
AB The successful control of HIV infection through either therapeutic agents or vaccines requires an extensive understanding of the agent itself and its pathogenesis. The fact that HIV is a member of the lentivirus subfamily of viruses was an immediate clue that the natural history of HIV infection would entail a lengthy latent period and disease progression, despite the generation of an immune response. Investigators have now characterized nine genes of HIV, including six regulatory genes which are thought to play an important role in the regulation of virus expression. The finding that the CD4 molecule is the receptor for HIV was instrumental in the recognition of the cell types particularly T4 lymphocytes and ***monocyte*** / ***macrophages*** , that are infected by HIV in vivo. The rapid variation in the HIV genome that occurs during virus replication may impact on the ability of the virus to escape immune surveillance as well as the apparent differences in isolate specific cell tropism. Although the exact processes by which HIV causes immunosuppression, neurological abnormalities, and other clinical manifestations are not known, it is clear that HIV can either kill T4 lymphocytes or render the cells functionally incompetent. Many studies have shown that the immunological abnormalities observed in HIV infection are not due solely to a depletion in CD4+ cells but to interference with the proper functioning of these cells as a result of virus binding to CD4 or through down-regulation of cellular gene function. Since the CD4+ T helper/inducer cell interacts with a myriad of other immune cells during the normal immune response, quantitative or qualitative changes in the T4 cell population have a pervasive effect on the immune system as a whole. Other cell types, such as ***monocyte*** / ***macrophages*** , bone marrow precursor cells, and Langerhans cells, may play an important part in the pathogenesis of HIV infection by functioning as reservoirs of HIV in the body and by infecting T4 cells during immune interactions. The question of why infection with HIV results in a long and variable asymptomatic period has not yet been adequately answered. Clearly, suppression or activation of viral regulatory genes is involved in HIV expression. Agents that have been shown to up-regulate HIV expression include mitogens, specific antigens, heterologous viruses, and cytokines that are invoked during normal human immune responses. Cytokines, mitogens, and heterologous viral genes have all been shown to up-regulate HIV expression via a trans-activating mechanism that acts on the HIV promoter sequences and is mediated by the binding of specific DNA-binding proteins to the HIV LTR. Five separate cellular protein-binding regions of the HIV LTR have been identified, implying that up-regulation of HIV expression may occur through several distinct mechanisms (Garcia et al., 1987). Activating agents may also up-regulate HIV expression by ***demethylating*** LTR enhancer sequences (Bednarik et al., 1987). At the same time that agents may be activating HIV expression, HIV infection may be affecting cellular gene expression. Neurological abnormalities, commonly found in HIV infection, can present in either a latent or active form both with or without immunological impairment. The precise mechanisms whereby HIV induces a wide range of neurological dysfunction are not well understood. Some hypotheses include the elaboration of cytotoxic factors from HIV-infected ***macrophages*** in the brain, interference with neurological transmitters or neurotropic factors, direct infection of neuronal cells, synergism between HIV and opportunistic viruses in the CNS of AIDS patients, and autoimmune phenomena. The role of the immune system in preventing or limiting infection with HIV is poorly understood. While many immune responses to HIV, such as the development of neutralizing antibodies, ADCC, ACC, and CTLs, have been delineated, the majority of HIV-infected individuals appear to follow an inexorable path to full-blown AIDS. the development of effective anti-HIV vaccines or immune system enhancers depends on a further understanding of a protective immune response. Although many questions have been answered with unprecedented speed, a greater understanding of the complex interactions between HIV and its host are clearly needed in order to effectively treat active infections and prevent the acquisition of new infections and the progression of latent infection to active disease. Further research into the pathogenesis of HIV infection using both in ***vitro*** experiments and in vivo studies in novel small-animal models, such as the severe combined immunodeficiency and transgenic models (Mosier et al., 1988; McCune et al., 1988a; J.M. Leonard et al., 1988; Namikawa et al., 1988), should continue to provide important insights for the control of AIDS in particular and other human diseases in general.

L30 ANSWER 27 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
23

AN 1989:200305 BIOSIS
DN BA87:101209
TI PERTURBATION OF STEROL BIOSYNTHESIS BY ITRACONAZOLE AND KETOCONAZOLE IN
LEISHMANIA-MEXICANA-MEXICANA INFECTED MACROPHAGES.
AU HART D T; LAUWERS W J; WILLEMSENS G; VANDEN BOSSCHE H; OPPERDOES F R
CS INTERNATL. INST. OF CELL. AND MOL. PATHOL., RES. UNIT FOR TROPICAL DIS.,
AVE. HIPPOCRATE 74, B-1200 BRUSSELS, BELGIUM.
SO MOL BIOCHEM PARASITOL, (1989) 33 (2), 123-134.
CODEN: MBIPDP. ISSN: 0166-6851.
FS BA; OLD
LA English
AB The azole antifungals ketoconazole and itraconazole possess in ***vitro*** antileishmanial activity against Leishmania mexicana mexicana amastigotes in ***macrophages*** (cell line J774G8). As in yeast and fungi, the activity is likely to be due to inhibition of the cytochrome P-450-dependent 14.alpha.- ***demethylation*** of lanosterol and/or 24,25-dihydrolanosterol. Indeed, 50% inhibition of ergosterol synthesis was observed at 0.21 .mu.M ketoconazole and 0.15 .mu.M itraconzole. At 5 .mu.M ketoconazole, traces of ergosterol could be found, whereas no ergosterol could be detected in cells treated with 5 .mu.M itraconazole. The inhibition of ergosterol biosynthesis was concomitant with an accumulation of the 14.alpha.-methylsterols lanosterol and 24,25-dihydrolanosterol. Fifty percent inhibition of cholesterol synthesis in unifected ***macrophages*** was achieved at 0.95 .mu.M and 1.5 .mu.M itraconazole and ketoconazole, respectively. In infected ***macrophages*** all [14C]acetate was incorporated in ergosterol, suggesting an inhibition in cholesterol synthesis in the host cells. An inhibition of ergosterol synthesis coincided with increasing cholesterol synthesis. The latter synthesis was inhibited at concentrations > 1 .mu.M. However, even at 5 .mu.M cholesterol synthesis was higher than under control conditions.

L30 ANSWER 28 OF 33 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 87107640 EMBASE
DN 1987107640
TI Methylation patterns of HLA-DR alpha genes in six mononuclear cell lines.
AU Wang Y.; Peterlin B.M.
CS Howard Hughes Medical Institute, University of California, San Francisco, CA 94143, United States
SO Immunogenetics, (1986) 24/5 (298-303).
CODEN: IMNGBK
CY Germany
DT Journal
FS 026 Immunology, Serology and Transplantation
022 Human Genetics
025 Hematology
LA English
AB The relationship between DNA methylation and HLA-DR(.alpha.) gene expression was investigated in six mononuclear cell lines. RPMI-4265 (B cell) and HUT-78 (T cell) constitutively express HLA-DR. HL-60 (myelomonocyte) and U-937 (***monocyte***) can be induced to express HLA-DR. Jurkat and Molt-4 (T cells) do not and cannot be induced to express HLA-DR. Based on the known nucleotide sequence of the HLA-DR(.alpha.) gene, methylation-sensitive restriction endonucleases Msp I, Hpa II, Hha I, Ava I, Hae II, and Sma I were used to detec t the CpG mehtylation in three regions of the HLA-DR(.alpha.) gene: the 5' flanking region, the exon 1 region, and the coding region containing exons 2, 3, 4, and 5. This precise mapping of CpG methylation yielded no correlation between DNA ***hypomethylation*** and HLA-DR(.alpha.) gene expression. In all cell lines, exon 1 region is ***hypomethylated*** , whereas 5' and coding regions are hypermethylated. Whereas hypermethylation of the coding region does not block transcription, ***hypomethylation*** of the exon 1 region may be essential but is clearly not sufficient for HLA-DR(.alpha.) gene transcription. This exon 1 region ***demethylation*** may result in an open (deoxyribonuclease I hypersensitive) chromatin conformation around the promoter where trans-acting regulatory factors presumably bind and initiate HLA-DR(.alpha.) transcription. In the course of this study, a novel Msp I polymorphism in the intron 1 of the HLA-DR(.alpha.) gene was found.

L30 ANSWER 29 OF 33 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 86000251 EMBASE
DN 1986000251
TI Chromatin structure of the c-myc gene in HL-60 cells during alterations of transcriptional activity.
AU Grosso L.E.; Pitot H.C.
CS Department of Oncology, McArdle Laboratory for Cancer Research, University of Wisconsin-Madison, Madison, WI 53706, United States
SO Cancer Research, (1985) 45/10 (5035-5041).
CODEN: CNREA8
CY United States
DT Journal
FS 016 Cancer
022 Human Genetics
LA English
AB HL-60 cells have an elevated level of cellular myc RNA due to an amplified c-myc gene. Subsequent to chemically induced differentiation of HL-60 cells, both cellular myc RNA levels and myc-specific transcription decrease. We have compared the primary DNA structure, DNA methylation, and S1 nuclease sensitivity of the myc protooncogene in HL-60 cells before and after chemically induced differentiation. We find no change in the structure or methylation of the c-myc gene. The protooncogene is ***hypomethylated*** at CCGG sequences in the 5' region but is extensively methylated at sites detected by sequences homologous to the 3' exon or 3' flanking sequences. Four S1 nuclease-sensitive sites are detected prior to differentiation. After the induction of either myeloid or ***monocytic*** differentiation, three of the S1 nuclease-sensitive sites are present. The presence of the fourth S1 nuclease-sensitive site correlates with the transcriptional activity of this gene.

L30 ANSWER 30 OF 33 MEDLINE DUPLICATE 24
AN 85264732 MEDLINE
DN 85264732 PubMed ID: 3874963
TI Metabolism of the nigrostriatal toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine by liver homogenate fractions.
AU Weissman J; Trevor A; Chiba K; Peterson L A; Caldera P; Castagnoli N Jr; Baillie T
NC DA-03405 (NIDA)
GM-07175 (NIGMS)
RR 09082 (NCRR)
SO JOURNAL OF MEDICINAL CHEMISTRY, (1985 Aug) 28 (8) 997-1001.
Journal code: J0F; 9716531. ISSN: 0022-2623.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198509
ED Entered STN: 19900320
Last Updated on STN: 19970203
Entered Medline: 19850912
AB The metabolic fate of the nigrostriatal toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has been examined in rat and rabbit liver mitochondrial and rabbit liver microsomal preparations. The mitochondrial preparations rapidly oxidized MPTP, in a pargyline-sensitive reaction, to a polar material that was shown to contain the 1-methyl-4-phenylpyridinium species as the principal product. NADPH-supplemented microsomal preparations converted MPTP to two principal products: 4-phenyl-1,2,3,6-tetrahydropyridine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine N-oxide. Carbon monoxide and SKF 525A selectively inhibited the oxidation of MPTP to the nor compound, indicating that this N- ***demethylation*** reaction is cytochrome P-450 catalyzed. Attempts to trap possible unstable iminium metabolites of MPTP in microsomal incubation mixtures with sodium cyanide led to the isolation of a ***monocyano*** adduct that proved to be the N-cyanomethyl derivative. Thus, hepatic mitochondrial and microsomal enzyme systems catalyze the oxidation of MPTP by different pathways, the former leading to the generation of species that may possess neurotoxic properties.

L30 ANSWER 31 OF 33 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 82182100 EMBASE
DN 1982182100
TI Derivation of macrophage-like lines from the pre-B lymphoma ABLS 8.1 using 5-azacytidine.
AU Boyd A.W.; Schrader J.W.
CS Walter and Eliza Hall Inst. Med. Res., Melbourne Hosp., Melbourne, Victoria 3050, Australia
SO Nature, (1982) 297/5868 (691-693).
CODEN: NATUAS
CY United Kingdom
DT Journal
FS 037 Drug Literature Index
026 Immunology, Serology and Transplantation
025 Hematology
016 Cancer
004 Microbiology
047 Virology
LA English
AB Variation in the degree of methylation of DNA seems to be one mode of regulation gene expression in eukaryotic cells. The relationship between DNA ***demethylation*** and gene activation observed in globin and viral genes, together with evidence that alterations in the degree of DNA methylation of a gene are heritable, although not with 100% fidelity, have suggested that this may be a mechanism of control of differentiation. Futhermore, exposure to the ***demethylating*** drug 5-azacytidine (5-AC) causes differentiation of 3T3 cells into striated muscle cells, chondrocytes and adipocytes. Subsequent studies have shown that these effects are due to DNA ***demethylation*** . In view of these observations, we have now attempted to modify several continuous B-cell lines with 5-AC. Following exposure of the pre-B lymphoma ABLS 8.1 to 5-AC, we have derived cloned cell lines which possess ***macrophage*** -like characteristics not expressed by ABLS 8.1. Similar ***macrophage*** -like cell lines were obtained in two independent experiments; they have been re-cloned and remain stable after 4 months of continuous culture.

L30 ANSWER 32 OF 33 MEDLINE
AN 77208701 MEDLINE
DN 77208701 PubMed ID: 874360
TI Cytochrome P-450 content and mixed-function oxidation by microsomes from rabbit alveolar macrophages.
AU Fisher A B; Huber G A; Furia L
SO JOURNAL OF LABORATORY AND CLINICAL MEDICINE, (1977 Jul) 90 (1) 101-8.

Journal code: IVR; 0375375. ISSN: 0022-2143.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 197708
ED Entered STN: 19900314
Last Updated on STN: 19900314
Entered Medline: 19770812
AB Cytochrome P-450 content and p-nitroanisole ***demethylation*** (a mixed-function oxidation) were investigated in the microsomal fraction from rabbit alveolar ***macrophages*** . The content of cytochrome P-450 was 0.13 +/- 0.024 (mean +/- S.E., n = 9) nmol/mg protein and was not stimulated by pretreatment of rabbits with chlorpromazine. Pretreatment with BCG resulted in decreased cytochrome P-450-specific content, suggesting that the microsomal protein pool was diluted by de novo synthesis of noncytochrome proteins. ***Demethylation*** of p-nitroanisole by alveolar ***macrophage*** microsomes during a 1 hr incubation was 17.1 +/- 1.4 nmol X hr-1 X mg protein-1. The microsomal fraction from homogenates of whole lungs had a cytochrome P-450 content of 0.32 +/- 0.078 nmol/mg protein and p-nitroanisole demethylase activity of 26.6 +/- 8.7 nmol X hr-1 X mg protein-1. The results indicate the presence of cytochrome P-450 in rabbit alveolar ***macrophages*** and show that the microsomal fraction can catalyze a mixed-function oxidation reaction. Comparison of alveolar ***macrophage*** and whole lung microsomal preparations indicates that alveolar ***macrophage*** cytochrome P-450 comprises a minor fraction of the total pulmonary pool.

L30 ANSWER 33 OF 33 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE 25
AN 1976:218784 BIOSIS
DN BA62:48784
TI RNA SYNTHESIS IN NORMAL AND IMMUNE MACROPHAGES AFTER ANTIGENIC STIMULUS.
AU SODERBERG L S F; TEWARI R P; SOLOTOROVSKY M
SO INFECT IMMUN, (1976) 13 (6), 1531-1538.
CODEN: INFIBR. ISSN: 0019-9567.
FS BA; OLD
LA Unavailable
AB ***Macrophage*** RNA synthesis is an important metabolic process intimately related to the function of these cells. Mouse peritoneal ***macrophages*** RNA was extracted with phenol in the presence of bentonite and electrophoresed on composite agarose-polyacrylamide gels. The pulse-chase technique was used to follow the precursor relationships in ***macrophage*** rRNA maturation. The rRNA species at 18S and 28S appeared at 15 and 45 min, respectively, after RNA synthesis was halted. Their appearance corresponded closely to decreases in the rRNA precursors at 45S, 36S, and 34S. Studies of RNA methylation aided in confirming the identity of these ribosomal species. ***Unmethylated*** RNA species appeared as mRNA between 5S and 15S, and at .apprx. 55S probably represented heterodisperse nuclear RNA. When normal ***macrophages*** were incubated with heat-killed Salmonella enteritidis, an acceleration in the maturation of RNA was observed. The accelerated maturation was indicated by the earlier appearance of 28S rRNA and the more rapid development of an equilibrium state; further labeling did not change the RNA profile. In ***macrophage*** RNA from mice immunized with S. enteritidis, rRNA species appeared rapidly but did not accumulate to the same extent as observed for normal ***macrophages*** . Precursor rRNA and other RNA species developed as usual, suggesting specific degradation of mature rRNA. Such rRNA wastage could indicate a mechanism controlling ribosome assembly in the non-proliferating activated ***macrophage*** . The pattern of RNA synthesis in immune ***macrophages*** was essentially unchanged by the presence of heat-killed S. enteritidis in ***vitro*** .

=> s 5 azacytidine or 2 deoxycytidine
L31 7850 5 AZACYTIDINE OR 2 DEOXYCYTIDINE

=> d his

(FILE 'HOME' ENTERED AT 14:18:30 ON 11 APR 2002)

FILE 'BIOSIS, MEDLINE, EMBASE' ENTERED AT 14:18:37 ON 11 APR 2002
E DE SANTIS/AU
L1 224 S DE SANTIS R/AU
L2 13 S DE SANTIS RITA/AU
L3 43464 S ANTIGEN PRESENTING CELL? OR APC
L4 27249 S HYPOMETHYLAT? OR DEMETHYLAT? OR UNMETHYLAT?
L5 52 S L3 (S) L4
L6 24 DUP REM L5 (28 DUPLICATES REMOVED)
L7 3494 S CANCER TESTIS ANTIGEN? OR CTA
L8 94 S L7 AND REVIEW
L9 64 DUP REM L8 (30 DUPLICATES REMOVED)
L10 152 S CANCER TESTIS ANTIGEN?
L11 7 S L10 AND REVIEW
L12 5 DUP REM L11 (2 DUPLICATES REMOVED)
L13 10042 S CANCER ASSOCIATED ANTIGEN? OR TUMOR ASSOCIATED ANTIGEN?
L14 24 S L7 AND L4
L15 11 DUP REM L14 (13 DUPLICATES REMOVED)
L16 4 S L13 AND L4
L17 2 DUP REM L16 (2 DUPLICATES REMOVED)
L18 3 S L1 AND REVIEW
L19 3 DUP REM L18 (0 DUPLICATES REMOVED)
L20 460 S L13 AND REVIEW
L21 349 DUP REM L20 (111 DUPLICATES REMOVED)
L22 0 S DENDRITIC CELL? AND L4 AND EX VIVO EXPAN?
L23 412 S L4 AND (DENDRITIC CELL? OR MACROPHAGE? OR MONOCY? OR ANTIGEN
L24 0 S EX VIVO EXPAN? AND L23
L25 0 S EX VIVO AND L23
L26 195 S ACTIVA? AND L23
L27 102 DUP REM L26 (93 DUPLICATES REMOVED)
L28 350 S L4 (2S) (DENDRITIC CELL? OR MACROPHAGE? OR MONOCY? OR ANTIGE
L29 75 S L28 AND (EX VIVO OR IN VITRO)
L30 33 DUP REM L29 (42 DUPLICATES REMOVED)
L31 7850 S 5 AZACYTIDINE OR 2 DEOXYCYTIDINE

=> s l31 and l23
L32 46 L31 AND L23

=> dup rem l32
PROCESSING COMPLETED FOR L32
L33 27 DUP REM L32 (19 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 27 ANSWERS - CONTINUE? Y/(N):y

L33 ANSWER 1 OF 27 MEDLINE DUPLICATE 1
AN 2001407474 MEDLINE
DN 21341709 PubMed ID: 11448917
TI Aberrant methylation of the adenomatous polyposis coli (***APC***) gene promoter 1A in breast and lung carcinomas.
AU Virmani A K; Rathi A; Sathyanarayana U G; Padar A; Huang C X; Cunnigham H
T; Farinas A J; Milchgrub S; Euhus D M; Gilcrease M; Herman J; Minna J D; Gazdar A F
CS Hamon Center for Therapeutic Oncology Research, and Department of Pathology, University of Texas Southwestern Medical Center, Dallas, Texas 75390-8593, USA.
NC 4P50CA7097-0452 (NCI)
P50CA7097 (NCI)
SO CLINICAL CANCER RESEARCH, (2001 Jul) 7 (7) 1998-2004.
Journal code: C2H; 9502500. ISSN: 1078-0432.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200110
ED Entered STN: 20011029
Last Updated on STN: 20011029
Entered Medline: 20011025
AB The adenomatous polyposis coli (***APC***) gene is a tumor suppressor gene associated with both familial and sporadic cancer. Despite high rates of allelic loss in lung and breast cancers, point mutations of the ***APC*** gene are infrequent in these cancer types. Aberrant methylation of the ***APC*** promoter 1A occurs in some colorectal and gastric malignancies, and we investigated whether the same mechanism occurs in lung and breast cancers. The methylation status of the ***APC*** gene promoter 1A was analyzed in 77 breast, 50 small cell (SCLC), and 106 non-small cell (NSCLC) lung cancer tumors and cell lines and in 68 nonmalignant tissues by methylation-specific PCR. Expression of the ***APC*** promoter 1A transcript was examined in a subset of cell lines by reverse transcription-PCR, and loss of heterozygosity at the gene locus was analyzed by the use of 12 microsatellite and polymorphic markers. Statistical tests were two-sided. Promoter 1A was methylated in 34 of 77 breast cancer tumors and cell lines (44%), in 56 of 106 NSCLC tumors and cell lines (53%), in 13 of 50 SCLC cell lines (26%), and in 3 of 68 nonmalignant samples (4%). Most cell lines tested contained the ***unmethylated*** or methylated form exclusively. In 27 cell lines tested, there was complete concordance between promoter methylation and silencing of its transcript. ***Demethylation*** with 5-aza- ***2*** '- ***deoxycytidine*** treatment restored transcript 1A expression in all eight methylated cell lines tested. Loss of heterozygosity at the ***APC*** locus was observed in 85% of SCLCs, 83% of NSCLCs, and 63% of breast cancer cell lines. The frequency of methylation in breast cancers increased with tumor stage and size. In summary, aberrant methylation of the 1A promoter of the ***APC*** gene and loss of its specific transcript is frequently present in breast and NSCLC cancers and cell lines and, to a lesser extent, in SCLC cell lines. Our findings may be of biological and clinical importance.

L33 ANSWER 2 OF 27 MEDLINE DUPLICATE 2
AN 2001567903 MEDLINE
DN 21488489 PubMed ID: 11602627
TI Dynamic DNA methylation change in the CpG island region of p15 during human myeloid development.
AU Sakashita K; Koike K; Kinoshita T; Shiohara M; Kamijo T; Taniguchi S; Kubota T
CS Department of Pediatrics, Institute of Organ Transplants, Reconstructive Medicine and Tissue Engineering, Shinshu University School of Medicine, 3-1-1, Asahi, Matsumoto, 390-8621, Japan.

SO JOURNAL OF CLINICAL INVESTIGATION, (2001 Oct) 108 (8) 1195-204.
Journal code: 7802877. ISSN: 0021-9738.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200112
ED Entered STN: 20011025
Last Updated on STN: 20020122
Entered Medline: 20011204
AB We examined the kenetics of p15 methylation and expression during myeloid development. We treated human cord blood CD34+ cells with either GM-CSF alone or in combination with stem cell factor and followed methylation at this locus using bisulfite genomic sequencing. CD34+ cells were found to be either fully methylated or completely ***unmethylated*** at 27 CpG dinucleotide sites in exon 1 and at 18 CpG sites in the promoter region of the p15 gene. A time-course study showed that the percentage of the allelic methylation of p15 CpG island increased to approximately 50% to 60% until 7 days after cytokine stimulation, then decreased to less than 10% after 21 days. The methylation was also observed in bone marrow CD34+ cells exposed to GM-CSF. p15 expression varied inversely with methylation. Expression was negligible or at low levels until 14 days, after which it increased substantially. The frequency of myeloid colony-forming cells in the progeny decreased and myeloid-specific markers increased in the later stages. Based on our observations on cells grown with GM-CSF and 5-aza- ***2*** '- ***deoxycytidine*** , DNA methylation of the p15 promoter region CpG island appears to be associated with proliferation rather than differentiation of normal human myeloid progenitors.

L33 ANSWER 3 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
3
AN 2002:194741 BIOSIS
DN PREV200200194741
TI Expression of neurotensin/neuromedin N precursor in murine mast cells.
AU Ahn, Hyun Jong; Cho, Jeong Je (1)
CS (1) Department of Microbiology, College of Medicine, Kyung Hee University, Hoegi-dong, Dongdaemun-gu, Seoul, 130-701: jjcho@khu.ac.kr South Korea
SO Korean Journal of Physiology & Pharmacology, (December, 2001) Vol. 5, No. 6, pp. 495-501. print.
ISSN: 1226-4512.
DT Article
LA English
AB We have cloned the mouse neurotensin/neuromedin N (NT/N) gene from the murine mast cell line C1.MC/C57.1 for the first time. The murine NT/N cDNA clone consisted of 765 nucleotides and coded for 169 peptide residues with an N-terminal signal peptide, and the C-terminal region contained of one copy of neurotensin (NT) and one copy of neuromedin N (NN). Total of four Lys-Arg dibasic motifs were present; one each at the middle of the open reading frame, at the N-terminal of NN, at the C-terminal of NT, and between NN and NT. Amino acid sequence analysis of the mouse NT/N revealed
90% homology to that of the rat NT/N gene. NT/N is expressed in routine mast cell lines (C1.MC/C57.1 and P815), but not in murine bone marrow-derived mast cells (BMMCs), murine ***macrophage*** cell line (RAW 264.7), nor in murine T cell line (EL-4). NT/N mRNA in C1.MC/C57.1 is highly inducible by IgE cross-linking, phorbol myristate acetate, neurotensin, and substance P. Following the treatment of ***demethylating*** agent, ***5*** - ***azacytidine*** (5-azaC), the NT/N gene was induced in BMMCs in response to IgE cross-linking. 5-azaC-treated BMMCs did not express the NT/N gene without additional stimuli. These findings suggested that the regulation of NT/N gene expression was dependent on the effects of not only gene methylation but also enhancer and/or repressor proteins acting on the NT/N promoter.

L33 ANSWER 4 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:437983 BIOSIS
DN PREV200100437983
TI Promoter methylation and inactivation of the adenomatous polyposis coli (***APC***) gene in breast and lung carcinomas.
AU Virmani, Arvind (1); Rathi, Asha; Sathyanarayana, Ubaradaka; Ashfaq, Raheela; Gilcrease, Micheal; Herman, James; Minna, John; Gazdar, Adi
CS (1) UT M.D. Anderson Medical Center, Houston, TX USA
SO Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2001) Vol. 42, pp. 398-399. print.
Meeting Info.: 92nd Annual Meeting of the American Association for Cancer Research New Orleans, LA, USA March 24-28, 2001
ISSN: 0197-016X.
DT Conference
LA English
SL English

L33 ANSWER 5 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
4
AN 2001:207400 BIOSIS
DN PREV200100207400
TI Sensitization by 5-aza- ***2*** '- ***deoxycytidine*** of leukaemia cells with MLL abnormalities to induction of differentiation by all-trans retinoic acid and 1alpha,25-dihydroxyvitamin D3.
AU Niitsu, Nozomi; Hayashi, Yasuhide; Sugita, Kanji; Honma, Yoshio (1)
CS (1) Saitama Cancer Centre Research Institute, 818 Komuro, Ina, Kita-adachi, Saitama, 362-0806: honma@cancer-c.pref.saitama.jp Japan
SO British Journal of Haematology, (February, 2001) Vol. 112, No. 2, pp. 315-326. print.
ISSN: 0007-1048.
DT Article
LA English
SL English
AB Most chromosomal abnormalities associated with breakage at 11q23 in acute leukaemia involve the MLL gene, and the presence of this breakage strongly predicts a poor clinical outcome. We assessed the possibility of differentiation-inducing therapy for acute leukaemias with chromosomal translocations involving 11q23. Among the cell lines with MLL translocations that we examined, KOCL48 and KOPN-1 cells were induced to differentiate into granulocytes by all-trans retinoic acid (ATRA) or into ***monocytes*** by 1alpha,25-dihydroxyvitamin D3 (VD3). These cells expressed p16 mRNA before treatment with 5-aza- ***2*** '- ***deoxycytidine*** (5-AZA), an inhibitor of DNA methylation. On the other hand, differentiation was not induced in SN-1, KOCL33, KOCL51 or KOCL44 cells by ATRA or VD3, and these cells did not express mRNA of this gene. However, these cells were effectively induced to differentiate by ATRA or VD3 in the presence of 5-AZA, and concomitantly exhibited p16 gene expression, suggesting an association between DNA ***demethylation*** and restoration of sensitivity to differentiation-inducing activity of ATRA or VD3 in leukaemia cells with MLL abnormalities. Based on these findings, combined treatment with ATRA or VD3 plus 5-AZA may be clinically useful in therapy for acute leukaemia with MLL abnormalities.

L33 ANSWER 6 OF 27 MEDLINE
AN 2001079845 MEDLINE
DN 21017431 PubMed ID: 11145021
TI Retrotransposable L1 elements expressed in rheumatoid arthritis synovial tissue: association with genomic DNA ***hypomethylation*** and influence on gene expression.
AU Neidhart M; Rethage J; Kuchen S; Kunzler P; Crowl R M; Billingham M E; Gay R E; Gay S
CS Center for Experimental Rheumatology, Department of Rheumatology, University Hospital, Zurich, Switzerland.
SO ARTHRITIS AND RHEUMATISM, (2000 Dec) 43 (12) 2634-47.
Journal code: 90M. ISSN: 0004-3591.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200101
ED Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010111
AB OBJECTIVE: Rheumatoid arthritis (RA) is characterized by a progressive destruction of joints by invasive synovial fibroblasts (SF). We searched for retroviral sequences in RA synovial fluid pellets, identified a sequence similar to that of open reading frame 2 (ORF2)/L1 retrotransposable elements, explored the expression of L1 in RA synovial tissues and cultured RA SF, and investigated the link to genomic DNA ***hypomethylation*** and the influence of functional L1 on gene expression. METHODS: RA synovial fluid pellets were screened by reverse transcriptase-polymerase chain reaction (RT-PCR) using degenerated pol primers. The sequences were identified by GenBank search. Riboprobes to ORF2/L1 and galectin-3 and antibodies to the ORF1/L1-related p40 protein were used for in situ hybridization and immunohistochemistry of synovial tissues and cultured RA SF. Real-time quantitative RT-PCR was used for detecting ORF1 messenger RNA (mRNA). Since DNA ***hypomethylation*** occurs in inflammatory diseases, we incubated cells with the methylation inhibitor 5-aza- ***2*** '- ***deoxycytidine*** (5-azaC) and compared RA SF and osteoarthritis (OA) SF. L1-negative RA SF were transfected with the functional L1.2 construct, and differential gene expression was analyzed by subtractive hybridization combined with nested PCR. RESULTS: RNA sequences similar to those of ORF2/L1 retrotransposable elements, THE1 transposon, human endogenous retrovirus (ERV)-E, human ERV-HC2, and gibbon
ape leukemia virus pol genes were isolated from different RA synovial fluid pellets. In RA synovial tissues, ORF2/L1 transcripts were detected in the sublining layer and at sites of cartilage and bone destruction. Galectin-3 mRNA and L1-related ORF1/ p40 protein showed similar expression patterns. In contrast, OA synovial tissues in situ and cultures in vitro were negative. Real-time quantitative RT-PCR confirmed the presence of ORF1 mRNA in cultured RA SF (30-300-fold the amount in normal SF), demonstrating the existence of a nondegenerated and functional L1 element. In vitro, the majority of RA SF expressed ORF2/L1 mRNA. After incubation of SF with 5-azaC, L1 mRNA appeared in a time- and dose-dependent manner. Compared with OA SF, RA SF were more sensitive to 5-azaC. After transfection of RA SF with a functional L1.2 element, human stress-activated protein kinase 2 delta (SAPK2delta [or SAPK4]), met protooncogene, and galectin-3 binding protein genes were differentially expressed. The transcription of the SAPK2delta gene, favored also by DNA ***hypomethylation*** in vitro, was confirmed in RA synovial tissues. CONCLUSION: Taken together, these data suggest that L1 elements and SAPK2delta pathways play a role in the activation of RA SF.

L33 ANSWER 7 OF 27 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2000083744 EMBASE
TI Low-dose 5-Aza- ***2*** '- ***deoxycytidine*** , a DNA ***hypomethylating*** agent, for the treatment of high-risk myelodysplastic syndrome: A multicenter phase II study in elderly

patients.
AU Wijermans P.; Lubbert M.; Verhoef G.; Bosly A.; Ravoet C.; Andre M.; Ferrant A.
CS Dr. P. Wijermans, Department of Haematology, Leyenburg Hospital, Leyweg 275, 2545 CH The Hague, Netherlands. hematey@worldonline.nl
SO Journal of Clinical Oncology, (2000) 18/5 (956-962).
Refs: 33
ISSN: 0732-183X CODEN: JCONDN
CY United States
DT Journal; Article
FS 016 Cancer
020 Gerontology and Geriatrics
025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Purpose: 5-Aza- ***2*** '- ***deoxycytidine*** (decitabine; DAC) is a DNA ***hypomethylating*** agent that has shown a 50% response rote in a small phase II study in elderly patients with high-risk myelodysplastic syndrome. We performed a second, multicenter phase II study in a larger group of patients to confirm our findings and to study the toxicity of DAC. Patients and Methods: Between June 1996 and September 1997, 66 patients (median age, 68 years) from seven centers received DAC 45 mg/m2/d for 3 days every 6 weeks. For patients in whom a complete response (CR) was reached after two courses, two further cycles were administered as consolidation therapy. In case of a stable disease situation, improvement, or a partial response (PR), a maximum of six cycles was administered. The primary end points were response rate and toxicity. The secondary end points were response duration, survival from the start of therapy, and overall survival. Results: The observed overall response rate was 49%, with a 64% response rate in the patients with an International Prognostic Scoring System (IPSS) high-risk score. The actuarial median response duration was 31 weeks, with a response duration of 39 weeks and 36 weeks for patients who reached a PR or CR, respectively. The actuarial median survival time from the time of diagnosis was 22 months and from the start of therapy was 15 months. For the IPSS high-risk group, the median survival time was 14 months. The median progression-free survival time was 25 weeks. Myelosuppression was rather common, and the treatment-related mortality rate was 7% and was primarily associated with pancytopenia and infection. Significant responses were observed with regard to megakaryopoiesis, with increases in platelet counts having already occurred after one cycle of DAC therapy in the majority of the responding patients. Conclusion: We were able to confirm our previous observation that DAC therapy was effective in half of the studied patients with high-risk myelodysplastic syndrome and is especially active in the patients with the worst prognoses. Myelosuppression was the only major adverse effect observed. (C) 2000 by American Society of Clinical Oncology.

L33 ANSWER 8 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:312490 BIOSIS
DN PREV200100312490
TI The treatment of 32D-BCR-ABL cells with 5-Aza- ***2*** ' ***deoxycytidine*** prior to GM-CSF slows proliferation and induces differentiation.
AU Davies, C. S. (1); Walsh, V. A. (1); Al-Sabah, A. I. (1); Hoy, T. (1); Burnett, A. K. (1); Mills, K. I. (1)
CS (1) Haematology, University of Wales College of Medicine, Cardiff UK
SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 352a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DT Conference
LA English
SL English
AB Chronic myeloid leukaemia (CML) is associated with the accumulation of large numbers of immature myeloid cells. As the disease progresses, these myeloid cells fail to differentiate. No definitive cause for this abnormal differentiation pattern has yet been determined, however, it is possible that abnormal methylation may be contributory factors in this process. The in vitro effect of the ***demethylating*** agent 5-Aza- ***2*** ' ***deoxycytidine*** (5AzaCdR) on the growth and differentiation of the murine myeloid cell line 32D and its BCR-ABL transformed counterparts, 32Db2a2 and 32Dp210 was investigated. Treatment with 5AzaCdR resulted in a decrease in cellular proliferation rate, which was most apparent in the BCR-ABL cell lines. This may be attributable to the activation of growth regulatory genes whose expression had been silenced by aberrant DNA methylation. This is supported, in the 32Dp210 cell line, by the induction in expression of the cell cycle regulatory gene p16INK4A following treatment with 5AzaCdR. Cell cycle analysis showed an increased proportion of cells in G0/1 following treatment with 5AzaCdR, which is consistent with the restoration of growth control. We examined whether ***demethylation*** , and possible induction of differentiation, mediated by 5AzaCdR rendered cells more responsive to the effects of GM-CSF. Treatment of 32Dp210 cells with 5AzaCdR prior to the differentiating agent GM-CSF restored growth control. This was accompanied by morphological and cell surface marker evidence of differentiation. An increased proportion of cells in G0/1 and a reciprocal decrease in cells in S phase was observed, consistent with the findings of differentiation induction. In summary, the pre-treatment of BCR-ABL transformed myeloid cells with 5AzaCdR leads to increased responsiveness to GM-CSF resulting in the loss of proliferative capacity and the generation of a more mature cell phenotype.

L33 ANSWER 9 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5
AN 2000:70910 BIOSIS
DN PREV200000070910
TI DNA methylation and chromatin structure regulate PU.1 expression.
AU Amaravadi, Lakshmi; Klemsz, Michael J. (1)
CS (1) Department of Microbiology and Immunology, Indiana University School of Medicine, 635 Barnhill Dr. MS5010, Indianapolis, IN USA
SO DNA and Cell Biology, (Dec.) Vol. 18, No. 12, pp. 875-884.
ISSN: 1044-5498.
DT Article
LA English
SL English
AB Knockout studies have shown that PU.1 is required for the normal development of many blood cell lineages, yet overexpression of this transcription factor in erythroid cells can lead to erythroleukemia. Thus, how the tissue-specific expression of PU.1 is regulated is important to our understanding of hematopoiesis. In this study, we showed that B and ***macrophage*** cell lines expressing PU.1 contained DNase I-hypersensitive sites in intron 1 and were ***hypomethylated*** at three MspI sites flanking exon 1. Results from studies using several T-cell lines suggested that the pattern of methylation changed as these cells matured. A pre-T cell line that expresses PU.1 contained DNase I-hypersensitive sites in intron 1 and was also ***hypomethylated*** at both MspI sites. Other immature T-cell lines had methylated at least one of the MspI sites and displayed no hypersensitive sites. Mature T-cell lines had a methylation pattern more similar to that of fibroblasts. Treatment of an immature T-cell line with ***5*** - ***azacytidine*** resulted in the expression of PU.1 transcripts. These data suggest that the tissue-specific expression of PU.1 is controlled by chromatin structure and DNA methylation and that this may be a mechanism used to shut off PU.1 expression in specific cell lineages during hematopoiesis.

L33 ANSWER 10 OF 27 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1999110875 EMBASE
TI [Myelodysplastic syndromes: New therapeutic approaches?].
SYNDROMES MYELODYSPLASIQUES: DE NOUVELLES APPROCHES THERAPEUTIQUES?.
AU Gardin C.; Dombret H.
CS C. Gardin, Service d'Hematologie Clinique, Hopital Beaujon, 100, boulevard du General-Leclerc, 92110 Clichy Cedex, France
SO Hematologie, (1999) 5/1 SUPPL. (32-34).
Refs: 13
ISSN: 1264-7527 CODEN: HEMAF2
CY France
DT Journal; Conference Article
FS 016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA French

L33 ANSWER 11 OF 27 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1998386905 EMBASE
TI Stem cell transplantation and intensified cytotoxic treatment for myelodysplasia.
AU Boogaerts M.A.
CS Dr. M.A. Boogaerts, University Hospital, Gasthuisberg, Herestraat 49, B 3000 Leuven, Belgium
SO Current Opinion in Hematology, (1998) 5/6 (465-471).
Refs: 38
ISSN: 1065-6251 CODEN: COHEF4
CY United States
DT Journal; General Review
FS 025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Substantial progress has been made in the understanding of the pathophysiology of the myelodysplastic syndromes. More refined prognostic classification systems have allowed more individualized treatment programs, leading to improved survival, but not at the expense of the quality of life of the patient. Recent data indicate that some high-risk myelodysplastic syndrome (MDS) patient categories, even some that only achieve partial remissions, may benefit from intensive cytotoxic treatment and may experience long-term survival. Newer chemotherapeutic regimens, eg, containing the mdr less sensitive Idarubicine, the purine analog fludarabine, or such ***hypomethylating*** agents as Decitabine, can lead to higher morphologic, cytogenetic, and molecular remission rates, providing a window of opportunity for the assessment of different forms of subsequent stem cell transplantation. Allogeneic stem cell transplantation from sibling donors remains the treatment of choice for younger intermediate and high risk patients with MDS. Much controversy, however, surrounds the applicability of this technique - certainly when using unrelated donors - as first line approach in younger low-risk patients with MDS. This has much to do with the often unacceptably high transplant related mortality rates. Autologous stem cell transplantation may provide

a suitable alternative for those patients without a suitable sibling donor or for older patient categories. Peripheral blood progenitor cell collections and transplantations are feasible and carry a low transplant related morbidity and mortality. Prospective randomized studies are underway to assess the true value of intensified chemotherapy with stem cell support in MDS. Childhood MDS is a rare disease, and the data on intensified cytotoxic treatment and transplantation are scarse. However, preliminary data are encouraging.

L33 ANSWER 12 OF 27 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 1999011970 EMBASE
TI Supportive care in hematologic malignancies.
AU Fetscher S.; Mertelsmann R.
CS Dr. S. Fetscher, Department of Internal Medicine, Division of Hematology and Oncology, Freiburg University Medical Center, Hugstetter Strasse 55, D-79106 Freiburg im Breisgau, Germany
SO Current Opinion in Hematology, (1998) 5/4 (271-286).
Refs: 91
ISSN: 1065-6251 CODEN: COHEF4
CY United States
DT Journal; General Review
FS 016 Cancer
025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Supportive care in hematologic malignancies includes a wide range of topics. We have selected the following issues for a review of recently published developments: new insights into the benefits and risks of established hematopoietic growth factors (HGF), such as granulocyte- or granulocyte- ***macrophage*** colony-stimulating factor (G-CSF, GM-CSF); the emerging role of newly introduced HGFs such as keratinocyte-growth factor (KGF) and thrombopoietin; the prophylactic and therapeutic use of amifostine, a cytoprotective agent; the role of hematopoietic growth factors and the ***demethylating*** agent decitabine in myelodysplastic syndromes (MDS); infectious complications of anticancer therapy; and, recent improvements in and complications of transfusional therapy, including the renewed interest in granulocyte transfusions.

L33 ANSWER 13 OF 27 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 97139706 EMBASE
DN 1997139706
TI Pharmacological approach for optimization of the dose schedule of 5-Aza- ***2*** '- ***deoxycytidine*** (Decitabine) for the therapy of leukemia.
AU Momparler R.L.; Cote S.; Eliopoulos N.
CS R.L. Momparler, Centre de Recherche Pediatrique, Hopital Ste-Justine, 3175 Chemin Cote Ste-Catherine, Montreal, Que. H3T 1C5, Canada
SO Leukemia, (1997) 11/SUPPL. 1 (S1-S6).
Refs: 57
ISSN: 0887-6924 CODEN: LEUKED
CY United Kingdom
DT Journal; Conference Article
FS 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB 5-Aza- ***2*** '- ***deoxycytidine*** (B-Aza-CdR; Decitabine) is an active antineoplastic agent in patients with leukemia. Since 5-Aza-CdR is an S phase specific agent and has a short plasma halflife, its antileukemic activity is dose schedule-dependent. Leukemia patients who are candidates for 5-Aza-CdR therapy following relapse after therapy with cytosine arabinoside are at greater risk for the problem of drug resistance-since these cytosine nucleoside analogues are metabolized by the same enzymes. Due to its unique mechanism of action of ***demethylating*** DNA, B-Aza-CdR has the potential to activate tumor (growth) suppressor and differentiation genes that have been accidentally silenced by DNA methylation in leukemic cells. All these factors should be taken into account in the design of the optimal dose schedule of this analogue. The optimal dose schedule of B-Aza-CdR should be based on the kinetic parameters of deoxycytidine kinase, its pharmacokinetics, its effects on DNA methylation and the cell cycle parameters of the leukemic cells and the normal hematopoietic stem cells. Since granulocytopenia is the major toxic effect produced by 5-Aza-CdR, the use of hematopoietic growth factors to shorten the duration of leukopenia should be investigated. Another approach which we are investigating is to use the methods of gene therapy to insert the cytidine deaminase gene into normal hematopoietic progenitor cells so as to make them drug resistant to B-Aza-CdR. The use of other agents that can induce the differentiation of leukemic cells in combination with B-Aza-CdR may have the potential to increase the clinical effectiveness of this analogue for the therapy of leukemia.

L33 ANSWER 14 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
6
AN 1996:538441 BIOSIS
DN PREV199699260797
TI Interleukin-3 increases the incidence of ***5*** - ***azacytidine*** -induced thymic lymphomas in pBOR-Il-3 mice.
AU Saavedra, Harold I. (1); Wang, Tzu-Hao; Hoyt, Peter R.; Popp, Diana; Yang, Wen K.; Stambrook, Peter J.
CS (1) Dep. Anat. Neurobiol. Cell Biol., Univ. Cincinnati Coll. Med., P.O. Box 670521, 231 Bethesda Ave., Cincinnati, OH 45267-0521 USA
SO Cellular Immunology, (1996) Vol. 173, No. 1, pp. 116-123.
ISSN: 0008-8749.
DT Article
LA English
AB Interleukin-3 (Il-3) is a glycoprotein produced by a CD4+CD8- subpopulation of T-lymphocytes. Il-3 has been associated with the proliferation of bone marrow stem cells and their differentiation to granulocytes, ***macrophages*** , basophil/mast cells, megakaryocytes, erythroid cells, and neutrophils. The pBOR-Il-3 transgenic mice were developed by pronuclear microinjection to study how chemical insults modulate transcription of the Il-3 gene driven by a long-terminal repeat (LTR) of an endogenous retrovirus and to determine the biological consequences of interleukin-3 expression. We injected ***5*** - ***azacytidine*** , a ***demethylating*** agent, to increase the LTR-driven expression of Il-3. Upon ***5*** - ***azacytidine*** treatment, both the pBOR-Il-3 and the FVB/N non-transgenic controls developed thymic lymphomas. The pBOR-Il-3 mice developed thymic lymphomas
at a higher frequency than the FVB/N mice. The thymic lymphoma cells were of a T-cell origin, as determined by T-cell receptor gene rearrangement analysis, and, in most cases, were of monoclonal origin. According to flow cytometric analysis of CD3, CD4, and CD8 cell surface markers, the thymic lymphoma cells did not lose their ability to differentiate, but the differentiation process was aberrant. Flow cytometric analyses also revealed that in pBOR-Il-3 mice the thymic lymphomas are mostly of a CD8+CD4- origin, whereas in the FVB/N group, the predominant type of thymic lymphoma is of a CD4+CD8- origin.

L33 ANSWER 15 OF 27 MEDLINE
AN 95226451 MEDLINE
DN 95226451 PubMed ID: 7536040
TI Transcriptional regulation of the mts1 gene in human lymphoma cells: the role of DNA-methylation.
AU Tulchinsky E; Grigorian M; Tkatch T; Georgiev G; Lukanidin E
CS Danish Cancer Society, Department of Molecular Cancer Biology, Copenhagen.
SO BIOCHIMICA ET BIOPHYSICA ACTA, (1995 Apr 4) 1261 (2) 243-8.
Journal code: A0W; 0217513. ISSN: 0006-3002.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199505
ED Entered STN: 19950524
Last Updated on STN: 19970203
Entered Medline: 19950515
AB The transcription of the mts1 gene putatively involved in the control of tumor metastasis was studied in three human lymphoma cell lines: MOLT-4, CEM and Jurkat. The level of the mts1 gene transcription is high in MOLT-4 cells, lower in CEM cells and hardly detectable in Jurkat cells. This correlates with the ***hypomethylation*** of DNA in the first exon and the first intron of the mts1 gene in the analyzed culture cells. This area was also found to be undermethylated in human peripheral blood cells--***macrophages*** , neutrophils and lymphocytes where the mts 1 gene is highly expressed. 5-Azadeoxycytidine (AzadC)--an inhibitor of the eukaryotic DNA-methylase--significantly induces the expression of the mts1 gene in CEM and Jurkat cells and has little effect on mts1 gene transcription in MOLT-4 cells. The drug does not influence mts1 transcription in cultivated peripheral blood lymphocytes. These data indicate the possible involvement of the methylation of the first exon/first intron sequences in the transcriptional repression of the mts1 gene. The finding of two DNAasel hypersensitivity sites (DHSs) mapped in the first intron of the mts1 gene supports this suggestion.

L33 ANSWER 16 OF 27 MEDLINE
AN 95254628 MEDLINE
DN 95254628 PubMed ID: 7537636
TI Suppression of intestinal neoplasia by DNA ***hypomethylation*** .
AU Laird P W; Jackson-Grusby L; Fazeli A; Dickinson S L; Jung W E; Li E; Weinberg R A; Jaenisch R
CS Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology, Cambridge 02142, USA.
NC F32 CA 09097 (NCI)
R35 CA 44339 (NCI)
SO CELL, (1995 Apr 21) 81 (2) 197-205.
Journal code: CQ4; 0413066. ISSN: 0092-8674.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199506
ED Entered STN: 19950615
Last Updated on STN: 19960129
Entered Medline: 19950602
AB We have used a combination of genetics and pharmacology to assess the effects of reduced DNA methyltransferase activity on ApcMin-induced intestinal neoplasia in mice. A reduction in the DNA methyltransferase

activity in Min mice due to heterozygosity of the DNA methyltransferase gene, in conjunction with a weekly dose of the DNA methyltransferase inhibitor 5-aza-deoxycytidine, reduced the average number of intestinal adenomas from 113 in the control mice to only 2 polyps in the treated heterozygotes. Hence, DNA methyltransferase activity contributes substantially to tumor development in this mouse model of intestinal neoplasia. Our results argue against an oncogenic effect of DNA ***hypomethylation*** . Moreover, they are consistent with a role for DNA methyltransferase in the generation of the C to T transitions seen at high frequency in human colorectal tumors.

L33 ANSWER 17 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1993:474277 BIOSIS
DN PREV199396107877
TI Megakaryocytic differentiation induced in 416B myeloid cells by GATA-2 and GATA-3 transgenes or ***5*** - ***azacytidine*** is tightly coupled to GATA-1 expression.
AU Visvader, Jane; Adams, Jerry M. (1)
CS (1) Walter and Eliza Hall Inst. Med. Research, PO Royal Melbourne Hosp., Parkville 3050 Australia
SO Blood, (1993) Vol. 82, No. 5, pp. 1493-1501.
ISSN: 0006-4971.
DT Article
LA English
AB The GATA 'zinc-finger' transcription factors are thought to have important roles in the control of hematopoiesis. GATA-1 and GATA-2 are found in the erythroid, mast cell, and megakaryocytic lineages, and GATA-3 in T lymphocytes. GATA-1 is required for erythroid development and has recently been shown by gene transfer to direct megakaryocytic differentiation of the primitive myeloid cell line 416B. Here we show that enforced expression in 416B cells of either the GATA-2 or GATA-3 gene also induces megakaryocytic differentiation, as assessed by cellular morphology, acetylcholinesterase activity, polyploid DNA content, and loss of Mac-1 expression. No erythroid or mast cell differentiation was found. Unexpectedly, the level of endogenous GATA-1 mRNA had increased 20- to 30-fold among the transfectants, whereas that of GATA-2 mRNA was unaltered and endogenous GATA-3 transcripts remained undetectable. This finding suggests that GATA-2 and GATA-3 lie upstream of GATA-1 in a regulatory hierarchy and that, in 416B cells, GATA-1 may mediate the phenotypic changes induced by GATA-2 or GATA-3. Furthermore, 416B cells treated with the DNA ***demethylating*** agent ***5*** - ***azacytidine*** underwent megakaryocytic differentiation accompanied by a marked increase in the level of GATA-1 mRNA but not that of GATA-2 or GATA-3. These results strongly implicate GATA factors in megakaryocytic differentiation and suggest that, at least for 41 6B cells, GATA-1 is a dominant regulator of maturation along this lineage.

L33 ANSWER 18 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1993:388736 BIOSIS
DN PREV199396064036
TI HLA-E is the only class I gene that escapes CpG methylation and is transcriptionally active in trophoblast-derived human cell line JAR.
AU Boucraut, Jose; Guillaudeux, Thierry; Alizadeh, Mehdi; Boretto, Joelle; Chimini, Giovanna; Malecaze, Francois; Semana, Gilbert; Fauchet, Renee; Pontarotti, Pierre; Le Bouteiller, Philippe (1)
CS (1) INSERM U100, CHU Purpan, F-31052 Toulouse Cedex France
SO Immunogenetics, (1993) Vol. 38, No. 2, pp. 117-130.
ISSN: 0093-7711.
DT Article
LA English
AB Polymorphic as well as HLA-F and -G genes are repressed in the human cell line JAR, derived from a tumor of trophoblast origin. By contrast, the HLA-E gene as well as the non-HLA novel coding-sequence, R1, located 5' to HLA-E, both remain transcriptionally active. We first demonstrated the role of DNA methylation in the repression of class I genes (except HLA-E) in JAR by the use of the ***5*** - ***Azacytidine*** ***demethylating*** agent. Following treatment, JAR clones reexpressed polymorphic class I transcripts and cell surface alpha chains. Using methylation-sensitive rare cutter enzymes on JAR genomic DNA, followed by classical or pulse field gel electrophesis and hybridization with HLA locus-specific probes, we found methylated CpG islands in the 5' region of all class I genes, except for HLA-E. These results, establishing an inverse relationship between stats of methylation and transcriptional activity within the MHC class I chromosomal region in JAR, and the observations that the HLA-E and R1 genes were ubiquitously expressed, suggest that the HLA-E chromosomal domain might have functional importance including the presence of housekeeping genes.

L33 ANSWER 19 OF 27 MEDLINE DUPLICATE 7
AN 93247309 MEDLINE
DN 93247309 PubMed ID: 7683359
TI Effects of 5-aza- ***2*** '- ***deoxycytidine*** on differentiation and oncogene expression in the human monoblastic leukemia cell line U-937.
AU Attadia V
CS Division of Experimental Oncology, Centro di Riferimento Oncologico, Aviano (PN), Italy.
SO LEUKEMIA, (1993 May) 7 Suppl 1 9-16.
Journal code: LEU; 8704895. ISSN: 0887-6924.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199306
ED Entered STN: 19930618
Last Updated on STN: 19970203
Entered Medline: 19930601
AB The DNA ***hypomethylating*** agent 5-aza- ***2*** '- ***deoxycytidine*** was able to induce irreversible terminal differentiation of the human monoblastic leukemia cell line U-937, when administered at a concentration of 0.1 microM every 12 hours for six times (72 hours). Differentiation occurred after removal of the drug, as shown by the gradual appearance of morphological, cytochemical, phenotypical, and functional cell maturation, along with the loss of the proliferative potential. Adherence to the plastic surface, a further marker of ***monocytic*** differentiation, was observed in long-term cultures of treated cells. Molecular events induced by 5-aza- ***2*** '- ***deoxycytidine*** included a decrease in DNA methylation, along with a dramatic, permanent reduction in the levels of c-myc transcripts; both these events were detectable early (24 to 48 hours) after the start of drug administration. A stable increase in c-fos and c-fms mRNAs, regarded as molecular markers of ***monocytic*** differentiation, was observed only after the end of treatment, in concomitance with the appearance of differentiation markers. The latency between early and late effects elicited by 5-aza- ***2*** '- ***deoxycytidine*** in U-937 cells suggests that the drug, presumably through DNA ***hypomethylation*** , is able to promote 'competence' to differentiate, via the activation of the regulatory program(s) needed for a monoblast to maturate, rather than directly inducing the expression of differentiation-specific genes. The temporal order of events described renders the present model suitable for the study of the human ***monocytic*** developmental program and of the molecular regulatory steps entailing differentiation by 5-aza- ***2*** '- ***deoxycytidine*** .

L33 ANSWER 20 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 1992:454908 BIOSIS
DN BA94:96308
TI ESTABLISHMENT VALIDATION AND EMPLOYMENT OF HUMAN PROMONOCYTE AND
T-LYMPHOCYTE CELL MODELS TO INVESTIGATE FACTORS THAT REGULATE HUMAN
IMMUNODEFICIENCY VIRUS TYPE 1 EXPRESSION.
AU PATEL P C; BOUCHARD J; VARIN M; RUSSO F; WALKER M C
CS IMMUNOL. RES. CENT., INST. ARMAND-FRAPPIER, 531 BLVD. DES PRAIRES, LAVAL,
QUEBEC H7V 1B7, CANADA.
SO IMMUNOL INFECT DIS (OXFORD), (1992) 2 (2), 119-125.
CODEN: IINDEK. ISSN: 0959-4957.
FS BA; OLD
LA English
AB A pair of stable transfectant cellular models for investigation of the regulation of human immunodeficiency virus type 1 (HIV-1) expression, one of human T-lymphocyte lineage and the other of human mononuclear phagocyte lineage were established, validated, and employed. To establish the cellular models, cells of the human promonocytic cell line U937 and the human T-cell line CEM-T4 were co-transfected by electroporation with DNA of the plasmid pU3R-III CAT containing the reporter gene chloramphenicol acetyltranferase (CAT) under the control of the HIV-1 long terminal repeat (LTR) and the plasmid pSV2Neo, to allow selection of transfectants by neomycin resistance. A clone of stably transfected cells of each cell type, designated as U937-2D4 and CEM-1D5 respectively, were selected as the two cellular models by the criteria of low-level constitutive expression of CAT activity and positive responsiveness in terms of an increase in CAT activity, following stimulation with phorbol myristate acetate, a known activator of the HIV-1 LTR in both T-cells and ***monocytic*** cells. To validate the utility of the two models in studying regulation of HIV-1 expression, U937-2D4 and CEM-1D5 cells were treated with cytokines and mitogens, previously determined either to activate the HIV-1 LTR through the nuclear binding factor NF-.kappa.B in both HIV infected T-cells and ***monocytes*** / ***macrophages*** (tumour necrosis factor .alpha.) or only in infected ***monocytic*** cells (lipopolysaccharide) or to activate HIV expression by mechanisms other than NF-.times.B binding (interleukin-6) only in ***monocytic*** cells. As anticipated, tumour necrosis factor .alpha. enhanced the CAT activity of both the 11937-2D4 and CEM-1D5 cells; whereas, lipopolysaccharide and interleukin-6 only increased the CAT activity levels of the U937-2D4 cells. The two cellular models were then employed to investigate the capacity of a ***demethylating*** agent, ***5*** - ***azacytidine*** , to activate the HIV-LTR. The CAT activity in both the U937-2D4 and CEM-1D5 cells, after exposure to ***5*** - ***azacytidine*** , was increased two to three times over the basal activity of untreated cells of the same model, supporting the hypothesis that DNA methylation is one of the mechanisms by which HIV expression is regulated.

L33 ANSWER 21 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
8
AN 1991:388731 BIOSIS
DN BA92:66046
TI DNA METHYLATION PROFILES IN THE HUMAN GENES FOR TUMOR NECROSIS FACTORS
ALPHA AND BETA IN SUBPOPULATIONS OF LEUKOCYTES AND IN LEUKEMIAS.

AU KOCHANEK S; RADBRUCH A; TESCH H; RENZ D; DOERFLER W
CS INST. GENETICS, COLOGNE, FRG.
SO PROC NATL ACAD SCI U S A, (1991) 88 (13), 5759-5763.
CODEN: PNASA6. ISSN: 0027-8424.
FS BA; OLD
LA English
AB The genomic sequencing technique has been applied to assess the state of methylation in the DNA from human leukocyte subpopulations from healthy individuals and in the DNA from several individuals with myeloid or lymphatic leukemias or non-Hodgkin lymphomas. Leukocyte populations were purified by the high-gradient magnetic cell sorting technique. In the human tumor necrosis factor .alpha. (TNF-.alpha.) gene segment between nucleotides 300 and 1150, the specific methylation profile in the DNA from human granulocytes and ***monocytes*** is maintained in three cases of myeloid leukemia. In one such case, all 5-methyl- ***2*** '-***deoxycytidine*** residues have been replaced by cytidine. In a chronic lymphatic T-cell leukemia, all 5-methyl- ***2*** '-***deoxycytidine*** residues have been substituted by cytidine. In normal B lymphocytes, in two cases of chronic lymphatic B-cell leukemias and two cases of non-Hodgkin lymphomas, all 5'-CG-3' sequences in this gene segment are devoid of methylation. In the TNF-.beta. gene, DNA methylation is decreased in several examples of acute or chronic myeloid leukemias in comparison to normal human granulocytes or ***monocytes*** , whose DNA is almost completely methylated between nucleotides 700 and 900. In human T and B lymphocytes, the main producers of TNF-.beta., in three instances of chronic lymphatic leukemias and two cases of non-Hodgkin lymphomas, all 5'-CG-3' sequences are ***unmethylated*** in this region. The DNA from the human HeLa cell line is highly methylated at all 5'-CG-3' sequences in the TNF-.alpha. and -.beta. genes. The TNF-.alpha. gene is transcribed in the cells of one case of acute myeloid leukemia in which the analyzed region of the TNF-.alpha. gene is completely ***unmethylated*** . The TNF-.beta. gene is not transcribed in any of the malignant cells tested.

L33 ANSWER 22 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
9
AN 1990:332161 BIOSIS
DN BA90:40180
TI CD4-POSITIVE CELLS TREATED WITH DNA METHYLATION INHIBITORS INDUCE
AUTOLOGOUS B CELL DIFFERENTIATION.
AU RICHARDSON B C; LIEBLING M R; HUDSON J L
CS UNIV. MICHIGAN, ANN ARBOR, MICHIGAN 48109-0531.
SO CLIN IMMUNOL IMMUNOPATHOL, (1990) 55 (3), 368-381.
CODEN: CLIIAT. ISSN: 0090-1229.
FS BA; OLD
LA English
AB The DNA methylation inhibitor ***5*** - ***azacytidine*** induces autoreactivity in cloned CD4+ T cells, but the functional consequences of this response are unknown. We now report that CD4+ T cells treated with ***5*** - ***azacytidine*** respond to autologous ***antigen*** - ***presenting*** ***cells*** and induce autologous B cell differentiation without exogenous antigen or mitogen. This mechanism could play a role in some autoimmune diseases characterized by T cell DNA ***hypomethylation*** and polyclonal B cell activation.

L33 ANSWER 23 OF 27 MEDLINE
AN 90111028 MEDLINE
DN 90111028 PubMed ID: 1688573
TI ***Unmethylation*** of specific sites in the 5' region is critical for the expression of murine alpha Fc gamma R gene.
AU Bonnerot C; Amigorena S; Fridman W H; Even J; Daeron M
CS Laboratoire d'Immunologie Cellulaire et Clinique, INSERM Unite 255, Institut Curie, Paris, France.
SO JOURNAL OF IMMUNOLOGY, (1990 Jan 1) 144 (1) 323-8.
Journal code: IFB; 2985117R. ISSN: 0022-1767.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 199002
ED Entered STN: 19900328
Last Updated on STN: 19960129
Entered Medline: 19900209
AB Three subtypes of murine low-affinity receptors for IgG (Fc gamma RII) have been identified. One is encoded by the alpha Fc gamma R gene, two are encoded by the beta Fc gamma R gene. In the present work, we examined whether DNA methylation might control expression of the alpha Fc gamma R gene. We found that, in DNA from a panel of Fc gamma R(+) and (-) cell lines, two MspI sites of the alpha Fc gamma R gene were selectively ***unmethylated*** only in the two cell lines containing alpha transcripts. These sites, separated by a distance of 1.2 kb, are located in the 5' region of the gene. All other MspI sites were methylated in all cell lines. Furthermore, ***5*** - ***azacytidine*** induced the ***demethylation*** and the expression of the alpha Fc gamma R gene in the Fc gamma R(-) thymoma BW5147. Both alpha Fc gamma R gene transcripts
and corresponding protein products became detectable in ***5*** - ***azacytidine*** -treated cells. The alpha Fc gamma R gene was also ***demethylated*** and expressed in mouse spleen cells cultured with human rIL-2. We conclude that a correlation links the ***unmethylation*** and the expression of the alpha Fc gamma R gene in murine cell lines as well as in nontransformed lymphoid cells responding to a physiological stimulus.

L33 ANSWER 24 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
10
AN 1988:461384 BIOSIS
DN BA86:103103
TI METHYLATION IN THE 5' REGION OF THE MURINE BETA FC-GAMMA-R GENE REGULATES
THE EXPRESSION OF FC-GAMMA RECEPTOR II.
AU BONNEROT C; DAERON M; VARIN N; AMIGORENA S; HOGARTH P M; EVEN J; FRIDMAN W
H
CS LABORATOIRE D'IMMUNOLOGIE CELLULAIRE ET CLINIQUE. UNITE INSERM 255-INST.
CURIE, 26, RUE D'ULM, 75231 PARIS CEDEX 05, FRANCE.
SO J IMMUNOL, (1988) 141 (3), 1026-1033.
CODEN: JOIMA3. ISSN: 0022-1767.
FS BA; OLD
LA English
AB In order to identify possible mechanisms regulating the expression of Fc.gamma.RII, we have examined the methylation status of the .beta. Fc.gamma.R gene in a panel of Fc.gamma.RII (+) and (-) cells belonging to several different lineages. We used .beta.1 cDNA probes, derived from .beta.Fc.gamma.R gene transcripts which encode murine Fc.gamma.RII molecules. We found that all CCGG sequences detected with these probes were methylated in the genomic DNA of the Fc.gamma.RII-(-) cells. By contrast, two CCGG sites were found to be selectively ***unmethylated*** in the DNA of all Fc.gamma.RII(+) cells tested. These sites could be assigned to the region of the 5' end of the .beta. Fc.gamma.R gene. Besides, the treatment of Fc.gamma.RII(-) thymoma cells BW5147 with ***5*** - ***azacytidine*** induced a ***hypomethylation*** of the .beta. Fc.gamma.R gene concomitantly with the transcription of that gene as seen by Northern blotting and the expression of functional Fc.gamma.RII. Conversely, the DNA-methylating agent ethyl methanesulfonate completely reversed the phenotype of the ***5*** - ***azacytidine*** -treated cells to that of the Fc.gamma.RII(-) BW5147 parent cells. In ethyl methanesulfonate-treated cells, the .beta. Fc.gamma.R gene was remethylated and the corresponding transcript was no more detectable. We conclude that the methylation of a specific 5' segment of the .beta. Fc.gamma.R gene regulates the expression of Fc.gamma.RII in murine T cells, B cells, mast cells, and ***macrophages*** , possibly by controlling the gene transcription.

L33 ANSWER 25 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
11
AN 1988:439986 BIOSIS
DN BA86:92084
TI INTERFERON-INDUCED EXPRESSION OF CLASS II MAJOR HISTOCOMPATIBILITY
ANTIGENS IN THE MAJOR HISTOCOMPATIBILITY COMPLEX MHC CLASS DEFICIENCY
SYNDROME.
AU PLAEGER-MARSHALL S; HAAS A; CLEMENT L T; GIORGI J V; CHEN I S Y; QUAN S G;
GATTI R A; STIEHM E R
CS DEP. PEDIATRICS, UCLA SCH. MED., LOS ANGELES, CALIF. 90024.
SO J CLIN IMMUNOL, (1988) 8 (4), 285-295.
CODEN: JCIMDO. ISSN: 0271-9142.
FS BA; OLD
LA English
AB Class II antigens encoded by genes of the major histocompatibility complex (MHC) are expressed by a variety of cell types and have a vital role in the cellular interactions required for an effective immune response. We have analyzed the regulation of HLA-DR, DP, and DQ class II antigen expression on cells of different lineage from an immunodeficient patient with the MHC class II deficiency syndrome. T and B lymphocytes, ***monocytes*** , and fibroblasts, which initially expressed no class II antigens, were treated with inductive stimuli that normally lead to enhanced expression of class II antigens. ***Monocytes*** , but not fibroblasts, cultured for 49-96 hr in the presence of recombinant gamma interferon expressed all three types of class II antigens. In contrast, T lymphocytes did not express class II antigens following their exposure to a variety of stimuli, including activation with phytohemagglutinin and culture in the presence of interleukin-2, transformation by the retrovirus HTLV-1 or HTLV-2 or exposure to the ***demethylating*** agent ***5*** - ***azacytidine*** . Similarly, class II antigens were not induced on B cells by cross-linkage of surface immunoglobulin molecules with anti-mu, exposure to Epstein-Barr virus, or treatment with soluble factors secreted by activated T cells. These results demonstrate that the regulation of class II MHC antigen expression by ***monocytes*** and lymphocytes is dissimilar and suggest that different regulatory genes are involved in the control of class II antigen expression by cells of different lineage.

L33 ANSWER 26 OF 27 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.DUPLICATE
12
AN 1984:339484 BIOSIS
DN BA78:75964

TI EXPRESSION OF HLA-DR BY A HUMAN ***MONOCYTE*** CELL LINE IS UNDER
TRANSCRIPTIONAL CONTROL.
AU PETERLIN B M; STOBO J D; GONWA T A
CS HOWARD HUGHES MED. INST., SAN FRANCISCO, CA 94143, USA.
SO JMCI (J MOL CELL IMMUNOL), (1984) 1 (3), 191-200.
CODEN: JMCIDI. ISSN: 0724-6803.
FS BA; OLD
LA English
AB The expression of Ia molecules by ***macrophages*** is not constitutive but can be enhanced by soluble factors from activated T cells. This induced expression of Ia appears to be causally important in certain accessory functions such as antigen presentation. While the phenomenon of Ia induction is clear, the mechanism by which this occurs has not been determined. Experiments were designed to investigate the molecular events leading to expression of the human Ia molecule, HLA-DR. The human ***monocytoid*** cell line U 937, which does not express any detectable HLA-DR molecules were used. Utilizing a cDNA [complementary DNA] probe for the .alpha. chain of HLA-DR and total cellular RNA, it could be demonstrated that resting U 937 lacked detectable HLA-DR transcripts. Digestion of genomic DNA from U 937 with the isoschizomers Msp I and Hpa II followed by analysis of the restriction fragments on Southern blots demonstrated the HLA-DR .alpha. chain genes to be methylated. Addition of ***5*** - ***azacytidine*** , an analog of cytidine which causes ***hypomethylation*** of DNA to U 937 caused ***hypomethylation*** of HLA-DR .alpha. chain genes but did not, by itself, lend to the appearance of HLA-DR molecules or transcripts. Treatment of U 937 with ***5*** - ***azacytidine*** followed by addition of either culture fluids from activated T cells or human recombinant .gamma. interferon did lead to the rapid appearance of abundant, mature HLA-DR transcripts and surface HLA-DR molecules. Methylation plays a role in the expression of human Ir genes. Induced expression of Ia molecules by soluble factors from T cells, including .gamma. interferon, is accompanied by the rapid appearance of Ir gene transcripts.

L33 ANSWER 27 OF 27 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 82182100 EMBASE
DN 1982182100
TI Derivation of ***macrophage*** -like lines from the pre-B lymphoma ABLS 8.1 using ***5*** - ***azacytidine*** .
AU Boyd A.W.; Schrader J.W.
CS Walter and Eliza Hall Inst. Med. Res., Melbourne Hosp., Melbourne, Victoria 3050, Australia
SO Nature, (1982) 297/5868 (691-693).
CODEN: NATUAS
CY United Kingdom
DT Journal
FS 037 Drug Literature Index
026 Immunology, Serology and Transplantation
025 Hematology
016 Cancer
004 Microbiology
047 Virology
LA English
AB Variation in the degree of methylation of DNA seems to be one mode of regulation gene expression in eukaryotic cells. The relationship between DNA ***demethylation*** and gene activation observed in globin and viral genes, together with evidence that alterations in the degree of DNA methylation of a gene are heritable, although not with 100% fidelity, have suggested that this may be a mechanism of control of differentiation. Futhermore, exposure to the ***demethylating*** drug ***5*** - ***azacytidine*** (5- AC) causes differentiation of 3T3 cells into striated muscle cells, chondrocytes and adipocytes. Subsequent studies have shown that these effects are due to DNA ***demethylation*** . In view of these observations, we have now attempted to modify several continuous B-cell lines with 5-AC. Following exposure of the pre-B lymphoma ABLS 8.1 to 5-AC, we have derived cloned cell lines which possess ***macrophage*** -like characteristics not expressed by ABLS 8.1. Similar ***macrophage*** -like cell lines were obtained in two independent experiments; they have been re-cloned and remain stable after 4 months of continuous culture.

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